

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 December 2001 (20.12.2001)

PCT

(10) International Publication Number
WO 01/95910 A1

(51) International Patent Classification⁷: **A61K 31/495**,
31/50, 31/52, 31/44, A61P 31/12, C07D 471/02, 473/30,
487/02

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(21) International Application Number: PCT/US01/14775

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(22) International Filing Date: 8 May 2001 (08.05.2001)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/211,447 13 June 2000 (13.06.2000) US
60/263,363 22 January 2001 (22.01.2001) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZOPYRIDINE AND IMIDAZOPYRIMIDINE ANTIVIRAL AGENTS

(57) Abstract: The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections. More particularly, the invention provides imidazopyridine and imidazopyrimidine derivatives (Formula I) for the treatment of respiratory syncytial virus infection.



WO 01/95910 A1

IMIDAZOPYRIDINE AND IMIDAZOPYRIMIDINE
ANTIVIRAL AGENTS

BACKGROUND OF THE INVENTION

5

1. **Field of the Invention**

The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections.

10 More particularly, the invention provides imidazopyridine and imidazopyrimidine derivatives (Formula I) for the treatment of respiratory syncytial virus infection.

2. **Background Art**

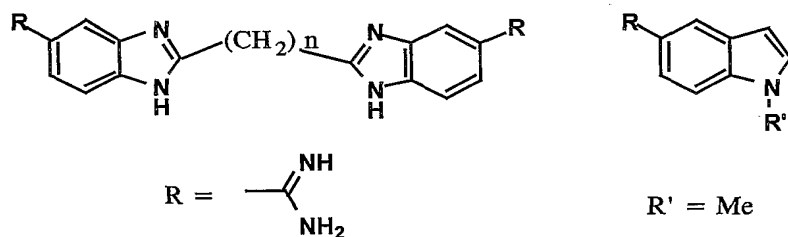
15 Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract infection in infants, children, elderly and immunocompromised persons. Severe infection of the virus may result in bronchiolitis or pneumonia which may require hospitalization or result in death. (*JAMA*, 1997, 277, 12). Currently only Ribavirin is approved for the treatment of this viral infection.

20 Ribavirin is a nucleoside analogue which is administered intranasally as an aerosol. The agent is quite toxic, and its efficacy has remained controversial. Other than Ribavirin, RespiGam and Synagis are an immunoglobulin and monoclonal antibody, respectively, that neutralize RSV. They are the only two

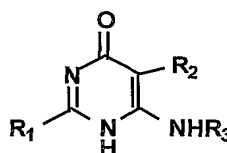
25 biologics that have been approved for prophylactic use in high risk pediatric patients for RSV infection. Both RespiGam and Synagis are very expensive and require parental administration.

Many agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, 7, 193). Y. Tao et al. (EP 0 058 146 A1, 1998)

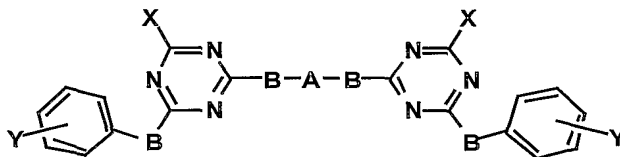
30 disclosed that Cetirizine, a known antihistamine, exhibited anti-RSV activity. Tidwell et al., *J. Med. Chem.* 1983, 26, 294 (US Patent 4,324,794, 1982), and Dubovi et al., *Antimicrobial Agents and Chemotherapy*, 1981, 19, 649, reported a series of amidino compounds with the formula shown below as inhibitors of RSV.



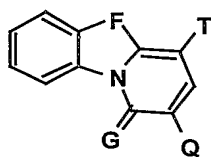
Hsu et al., US Patent 5,256,668 (1993) also disclosed a series of 6-aminopyrimidones that possess anti-viral activity against RSV.



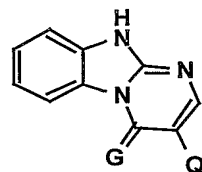
In addition, Y. Gluzman, et al., (AU Patent, Au-A-14,704, 1997) and P. R. Wyde et al. (*Antiviral Res.* 1998, 38, 31) disclosed a series of triazine containing compounds that were useful for the treatment and/or prevention of RSV infection.



Another series of compounds structurally related to this invention are pyrido[1,2-a]benzoazoles and pyrimidio[1,2a]benzimidazoles disclosed by S. Shigeta et al in *Antiviral Chem. & Chemother.* 1992, 3, 171. These compounds have demonstrated inhibition of orthomyxovirus and paramyxovirus replication in HeLa cells. The structures of these compounds are shown in formulas Id and Ie, in which $F = NH, S, \text{ or } O$; $Q = -NHCOPh, -COOH, COOEt, \text{ or } CN$; $T = COMe, CN, \text{ or } COOEt$; $G = O \text{ or } NH$.

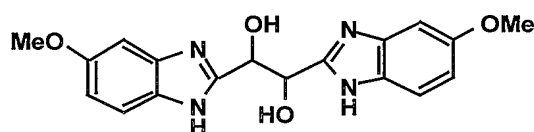


Formula Id

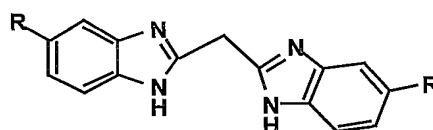


Formula Ie

A bis-benzimidazole with an ethylenediol linker shown below has also been reported as a potent inhibitor of rhinoviruses (Roderick, et al. *J. Med. Chem.* 1972, 15, 655).

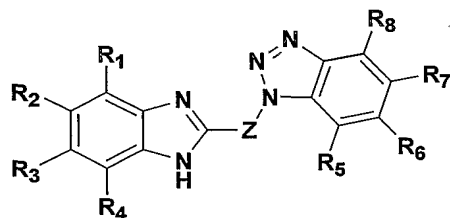


Other structurally related compounds are bis-benzimidazoles which possess antifungal activity (B. Cakir, et al. *Eczacilik Fak. Derg.* 1988, 5, 71).

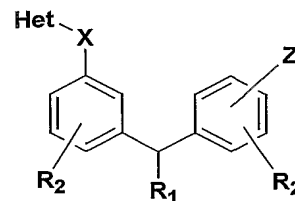


R = H, NO₂

Most recently Yu et al. have discovered a series of benzimidazoles (Formula II) for the treatment and prevention of RSV infection (WO 00/04900). In addition, Theodore Nitz has also found a series of compounds with Formula III that inhibit RSV in Hep-2 cell tissue culture assay (WO 99/38508). Although many other agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, 7, 193) none of them have been used in human clinical trials. Thus, there is a medical need for a convenient and less expensive anti-viral agent for the treatment and prevention of RSV infection.



Formula II

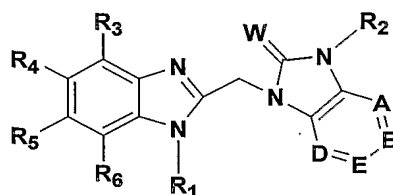


Formula III

5

SUMMARY OF THE INVENTION

This invention relates to compounds having the Formula I, and pharmaceutically acceptable salts thereof



Formula I

10

wherein:

15 W is O or S;

R₁ is -(CR'R'')_n-X;

X is H, C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR''', NR'R'', NR'COR'', NR'CONR''R''', NR'SO₂R'', NR'COOR'', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', PO(OR')₂, aryl, heteroaryl or non-aromatic heterocycle;

25

m is 0-2; n is 2-6;

R₂ is

(i) H, C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, -(CH₂)_t C₃₋₇ cycloalkyl, -(CH₂)_t C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is 1-6;

(ii) -(CR'R")_n-Y, wherein Y is CN, OR', OCONR'R", NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR'R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂; wherein

m is 0-2 and n' is 1-6;

(iii) -(CR'R")_n-C₆H₄-Z, wherein the Z group may be in the ortho, meta or para position relative to the -(CH₂)_n group; Z is CN, OR', OCONR'R", NO₂, NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR'R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂;

m is 0-2; n" is 0-6; or

(iv) -(CR'R")_{n'''}-heteroaryl, wherein n''' is 0-6;

(v) -(CR'R")_{n'''}-non-aromatic heterocycle, wherein n''' is 0-6;

R₃, R₄, R₅ and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkyl substituted with one to six of the same or different halogen atoms, OR', CN, COR', COOR', CONR'R", or NO₂;

A, B, E, D are each independently C-H, C-Q-, N, or N-O; provided at least one of A, B, E or D is not C-H or C-Q; wherein Q is halogen, C₁₋₃ alkyl or C₁₋₃ alkyl substituted with one to three of the same or different halogen atoms; and

R', R'', R''' are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; or R' and R'' taken together form a cyclic alkyl group
5 having 3 to 7 carbon atoms; benzyl or aryl ;

R'''' is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, NR'R'', CR'NR''', aryl, heteroaryl, non-aromatic heterocycle; and

10 Non-aromatic heterocycle is a 3-7 membered non-aromatic ring containing at least one and up to 4 non-carbon atoms selected from the group consisting of O, S, N, and NR';

Aryl is phenyl, naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl;

15

Heteroaryl is a 4-7 membered aromatic ring which contains one to five heteroatoms independently selected from the group consisting of O, S, N or NR', wherein said aromatic ring is optionally fused to group B';

20 B' is an aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl;

Aryl, B', said 4-7 membered aromatic ring, and said 3-7 membered non-aromatic ring may each independently contain one to five substituents which are each

25 independently selected from R₇, R₈, R₉, R₁₀ or R₁₁; and

R₇, R₈, R₉, R₁₀ and R₁₁ are each independently

(i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; and

- 5 (ii) halogen, CN, NO₂, OR', NR'R'', COR', COOR', CONR'R'', OCOR', NR'COR'', SO_mR', SO₂NR'R'', PO(OR')₂.

A preferred embodiment includes compounds of Formula I wherein heteroaryl is selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, 10 pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, 15 benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, tetrazole and phenoxazinyl.

20 Another preferred embodiment includes compounds of Formula I wherein:

R₁ is -(CH₂)_n-X;

X is H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, 25 each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR'', NR'R'', NR'COR'', NR'COOR'', COR', CR''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', aryl or heteroaryl;

30 m is 0-2; n is 2-4;

R₂ is

(i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, -(CH₂)_t C₃₋₇ cycloalkyl, -(CH₂)_t C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of
5 the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is 1-6;

(ii) -(CH₂)_n-Y, wherein Y is CN, OR', COR', COOR', CONR'R", SO_mR', SO₂NR'R", PO(OR')₂ wherein m is 0-2 and n' is 1-6; or
10

(iii) -(CH₂)_{n''}-C₆H₄-Z, wherein the Z group may be in the ortho, meta or para position relative to the -(CH₂)_{n''} group; Z is CN, OR', COR' or SO_mR'; m is 0-2; n'' is 0-3;

15 R₃, R₄, R₅, and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, optionally substituted with one to six of the same or different halogen atoms; and

A, B, E, D are each independently C-H or N; provided at least one of A, B, E or D is not C-H.

20

Another preferred embodiment includes compounds of Formula I wherein:

R₃, R₄, R₅ and R₆ are each H;

25 A, B and D are each C-H; and

E is N.

Another preferred embodiment includes compounds of Formula I wherein:

30

R₃, R₄, R₅ and R₆ are each H;

A, B and E are each C-H; and

D is N.

5 In another embodiment of the invention there is provided a method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of one or more of the aforementioned compounds of having Formula I, including pharmaceutically acceptable salts thereof.

10 Another embodiment includes a pharmaceutical composition which comprises a therapeutically effective amount of one or more of the aforementioned anti-RSV compounds having Formula I, including pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

15 The term pharmaceutically acceptable salt includes solvates, hydrates, acid addition salts and quarternary salts. The acid addition salts are formed from a compound of Formula I and a pharmaceutically acceptable inorganic or organic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric, 20 methanesulfonic, acetic, citric, malonic, fumaric, maleic, oxalic acid, sulfamic, or tartaric acids. Quaternary salts include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, oxalate, sulfamate, and tartrate. Halogen means bromine, chlorine, fluorine and iodine.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply unless indicated otherwise:

5 An “aryl” group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl.

10 As used herein, a “heteroaryl” group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, 15 imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzthiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, and pyrazinyl.

20 As used herein, a “non-aromatic heterocycle” group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of non-aromatic heterocycle 25 groups are azetidiny, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, oxazolidonyl, oxazolonyl, 2-pyrrolidinonyl, hydantoinyl, meleimidyl and oxazolidinedionyl.

30 An “alkyl” group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., “1-20”, is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More

preferably, it is a medium size alkyl having 1 to 10 carbon atoms. For example, the term "C₁₋₆ alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

5

A "cycloalkyl" group refers to a saturated all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system.

Examples, without limitation, of cycloalkyl groups are cyclopropane,

10 cyclobutane, cyclopentane, cyclohexane, cycloheptane, and adamantane.

A "cycloalkenyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings contains one or more carbon-carbon double bonds but does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkenyl groups are cyclopentene, cyclohexadiene, and cycloheptatriene.

15

An "alkenyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond.

20

An "alkynyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an -OH group.

25

An "alkoxy" group refers to both an -O-alkyl and an -O-cycloalkyl group as defined herein.

An "O-carboxy" group refers to a R^{''}C(O)O-group, with R^{''} as defined herein.

30

An "amino" group refers to an -NH₂ group.

A "N-amido" group refers to a $R^x C(=O)NR^y$ - group, with R^x selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heteroalicyclic and R^y selected from hydrogen or alkyl.

5 A "cyano" group refers to a $-CN$ group.

It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well
10 understood by chemists in the art. The disclosure and claims of the present invention are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

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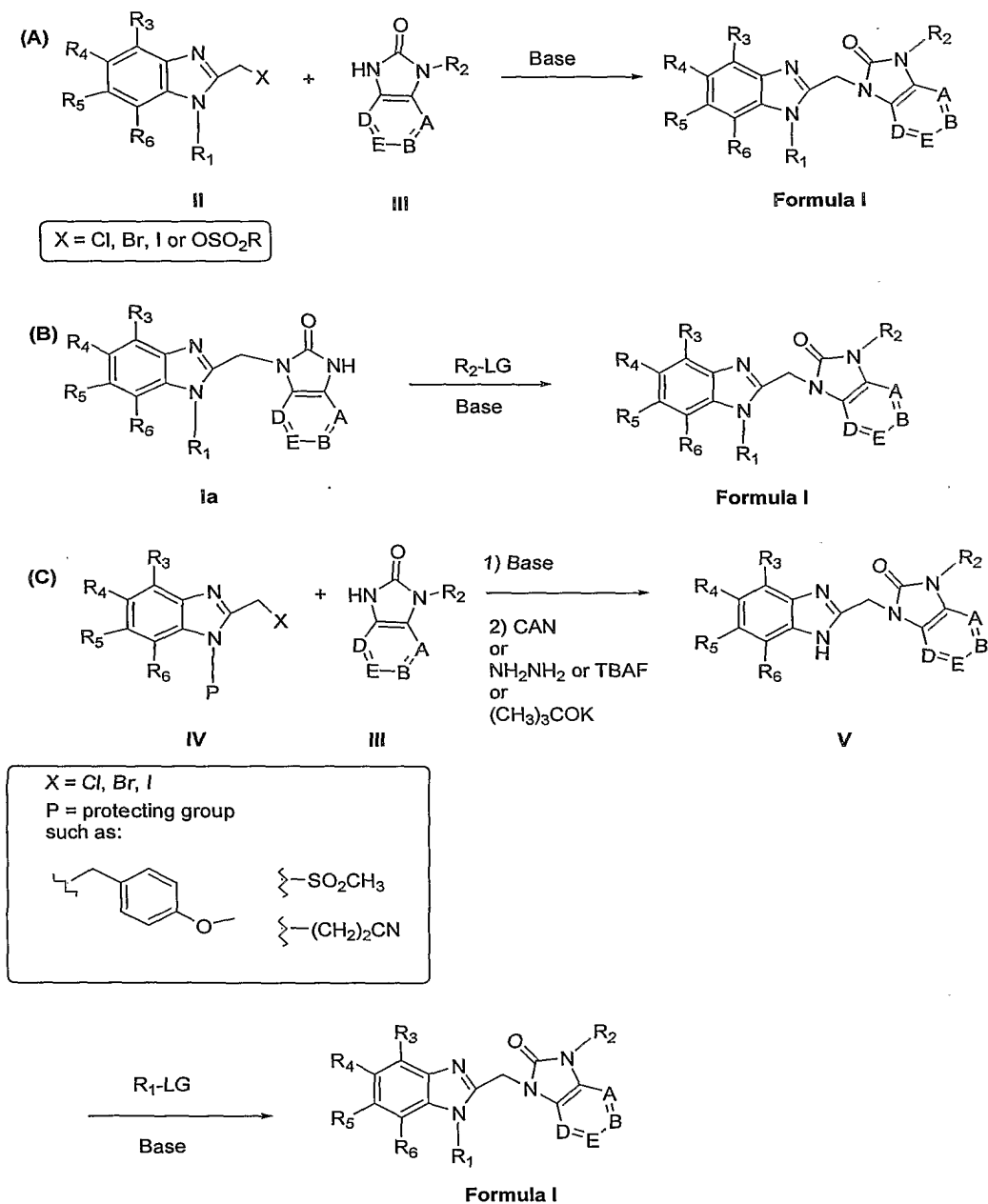
Compounds of Formula I can be prepared either by coupling 2-substituted-benzimidazoles (II), where X is a halide or sulfonate such as mesylate or tosylate, with 2-oxo-imidazopyridines or 2-oxo-imidazopyrimidines (III) in the presence of base, preferably phosphazene bases such as t-butyylimino-tri(pyrrolidino)phosphorane (BTPP), cesium carbonate or sodium hydride
20 (Scheme I-A) or by reacting Ia with a R_2-LG , where LG is a leaving group, preferably a halide or sulfonate such as mesylate or tosylate (Scheme I-B). Alternatively, compounds of Formula I can be synthesized according to the procedure described in Scheme I-C. Coupling of 2-substituted-benzimidazoles (IV) containing protecting groups (P) such as p-methoxybenzyl, mesyl, or 2-cyanoethyl with 2-oxo-imidazopyridines or 2-oxo-imidazopyrimidines in the presence of base is followed by removal of the protecting group using appropriate conditions. Deprotection can be accomplished by treatment with ceric ammonium nitrate (CAN), treatment with hydrazine or tetrabutylammonium
25 fluoride (TBAF), or treatment with potassium *tert*-butoxide to respectively remove p-methoxybenzyl, mesyl, or 2-cyanoethyl groups and give intermediates V. Compounds of Formula I can then be prepared by reacting V with R_1-LG

30

where LG is a leaving group preferably a halide or sulfonate such as mesylate or tosylate.

Scheme I: Preparation of Formula I

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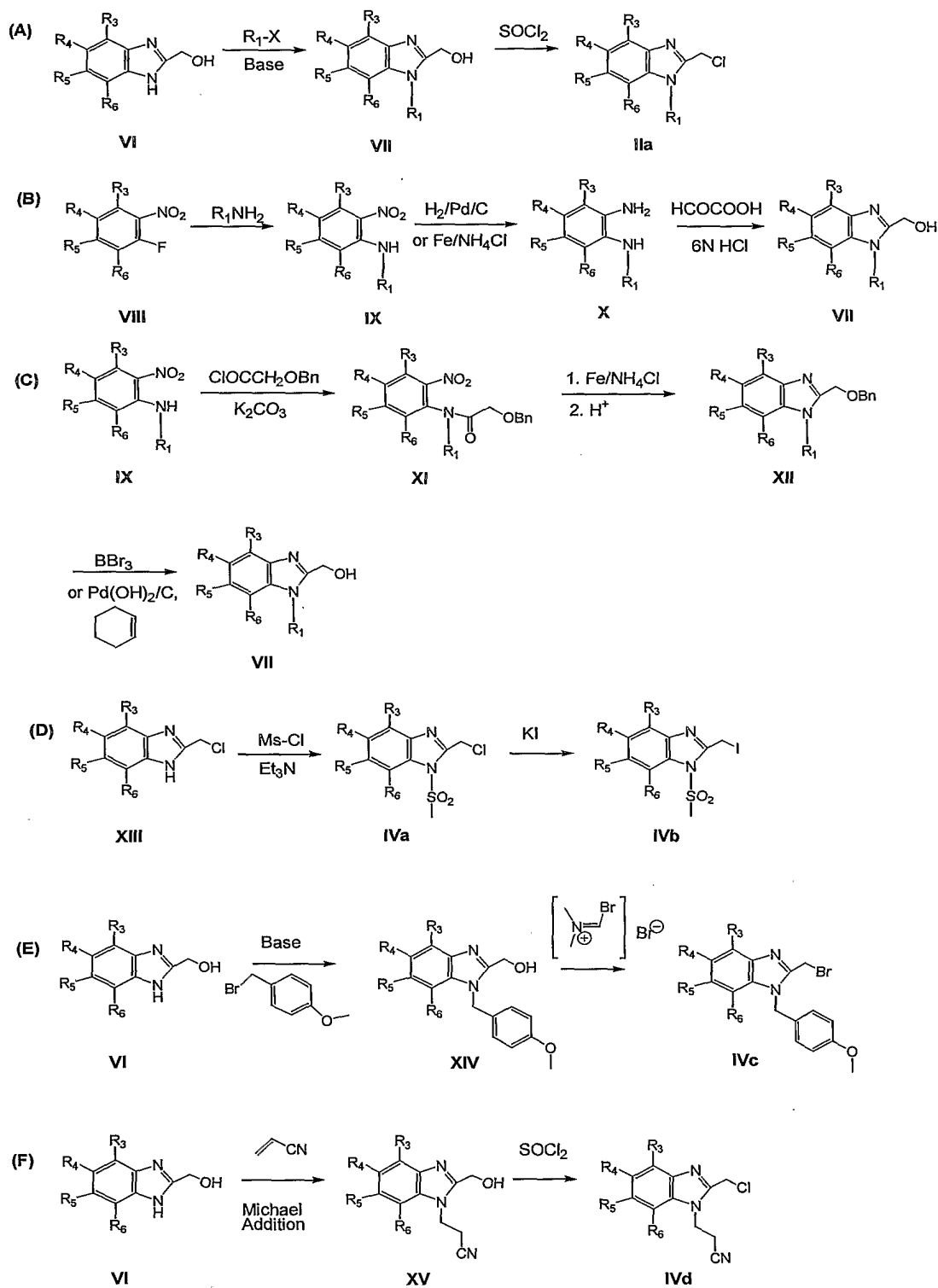


The synthesis of 2-substituted-benzimidazoles (IIa) is shown in Schemes II A-C. Treatment of substituted or unsubstituted 2-hydroxymethylbenzimidazole

- (VI) with 1.05 equivalents of base, preferably sodium hydride or cesium carbonate, followed by the addition of R₁-LG, where LG is a leaving group such as halide or sulfonate, gives compound VII. Treatment of the alcohol with thionyl chloride provides 2-chloromethyl-benzimidazole IIa (Scheme II-A). In a separate synthetic route, depicted in Scheme II-B, 2-fluoro-nitrobenzene (VIII) reacts with an amine to afford compound IX. Reduction of the nitro group provides a phenylenediamine derivative X which is cyclized with glycolic acid in 4-6 N HCl to give alcohol VII. Alternatively, 2-amino-nitrobenzene (IX) is acylated with 2-benzyloxyacetyl chloride to provide XI (Scheme II-C).
- 10 Reduction of the nitro group followed by ring closure in ethanol in the presence of catalytic amount of acetic acid provides XII. Removal of the benzyl group using boron tribromide or palladium hydroxide on carbon and cyclohexene yields VII.

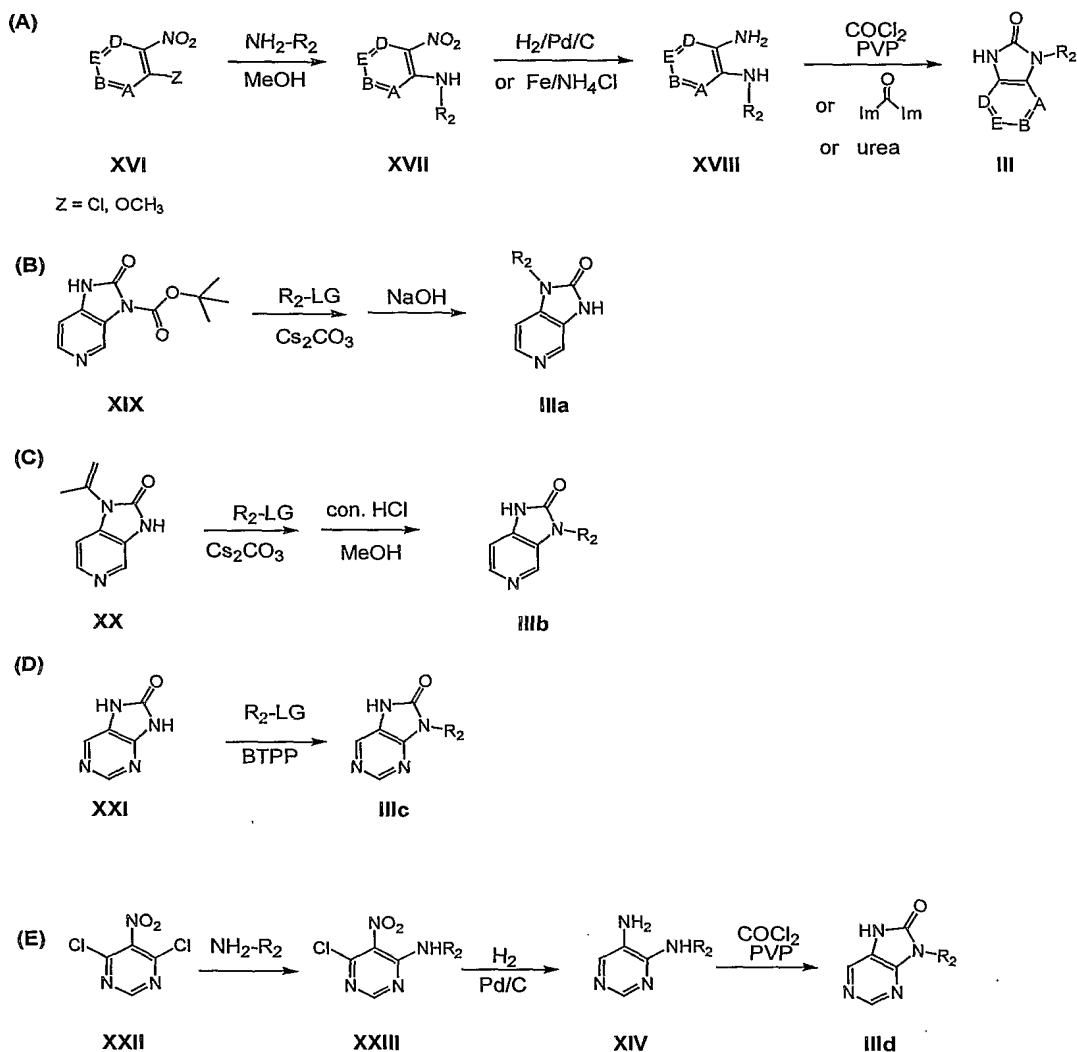
- Preparation of compounds IVa – IVd containing protecting groups is depicted in Schemes II D-F. In Scheme II-D, 2-chloromethylbenzimidazole reacts with methane sulfonyl chloride (Ms-Cl) and triethylamine to give compound IVa. The chloride can be refluxed with potassium iodide in acetone to produce compound IVb. A *p*-methoxybenzyl protecting group is installed in Scheme II-E. Reaction of 4-methoxybenzyl chloride with 2-hydroxymethyl benzimidazole (VI) in the presence of base, preferably sodium hydride, gives compound of Formula XIV. Treatment of alcohol XIV with (bromomethylene)dimethylammonium bromide provides compound IVc. Compound IVd can be prepared as described in Scheme II-F. Michael addition of 2-hydroxymethylbenzimidazole (VI) with acrylonitrile yields compound XV
- 25 which is then converted to the chloride IVd by treatment with thionyl chloride.

Scheme II: Preparation of Benzimidazoles Ia



2-Oxo-imidazopyridines and 2-oxo-imidazopyrimidines can be synthesized using the procedure depicted in Scheme III. Displacement of Z, which is a halide, preferably chlorine, or an alkoxy group, preferably methoxy, of nitropyridines **XVI** (2-chloro-3-nitro-pyridine, 4-alkoxy-3-nitropyridine and 3-alkoxy-2-nitropyridine) with an amine gives **XVII** (Scheme III-A). Reduction of the nitro group and cyclization of the resulting diamine (**XVIII**) using phosgene/polyvinylpyridine, carbonyldiimidazole or urea provides N3-substituted 2-oxo-imidazopyridine **III**. N-substituted 2-oxo-5-imidazo-pyridines **IIIa** are prepared from known compound **XIX** by N-alkylation and deprotection of the *t*-butoxycarbonyl with aqueous sodium hydroxide (Scheme III-B). On the other hand, N-alkylation of **XX** and acid hydrolysis of the isopropenyl group gives 2-oxo-imidazo-6-pyridine **IIIb** (Scheme III-C). 2-Oxo-imidazopyrimidines (**IIIc**) can be prepared directly by reacting 2-oxo-imidazopyrimidine (**XXI**) with R₂-LG where LG is a leaving group as described above, to give **IIIc**, as illustrated in Scheme III-D. Alternatively, 4,6-dichloro-5-nitropyrimidine (**XXII**) is treated with an amine to generate **XXIII** (Scheme III-E). Catalytic reduction of both the nitro group and the carbon-chlorine bond, and cyclization of the resulting diamine (**XIV**) with phosgene provides **IIId**.

Scheme III: Preparation of 2-oxo-imidazopyridines and 2-oxo-imidazopyrimidines



5

Experimental Section

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker Avance 500, AC-300, Bruker DPX-300 or a Varian Gemini 300 spectrometer. All spectra were determined in CDCl₃, CD₃OD, or DMSO-d₆ and chemical shifts are reported in δ units relative to tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets; dt, doublet of triplets. Mass

spectroscopy was performed on a Finnigan SSQ 7000 quadrupole mass spectrometer in both positive and negative electrospray ionization (ESI) modes or on a LC-MS using Shimadzu LC-10AS with micromass platform LC single quadrupole mass spectrometer in positive electrospray ionization. High resolution mass spectroscopy was recorded using a Finnigan MAT 900. Infrared (IR) spectra were recorded on a Perkin-Elmer system 2000 FT-IR. Elemental analysis was performed with a Perkin-Elmer series II, model 2400 CHN/O/S analyzer. Column chromatography was performed on silica gel from VWR Scientific. Preparative HPLC was performed using a Shimadzu LC-8A on a C18 column eluted with mixture of MeOH in water with 0.1 % trifluoroacetic acid.

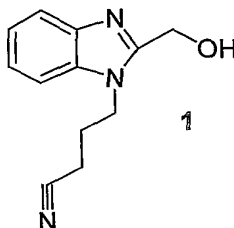
Abbreviations used in the experimental section:

BEMP: 2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
BTPP: *t*-butylimino-tri(pyrrolidino)phosphorane
CAN: ceric ammonium nitrate
DBU: 1,8-diazabicyclo[5,4,0]undec-7-ene
DIEA: *N,N*-diisopropylethylamine
DMF: dimethylformamide
DMSO: dimethyl sulfoxide
Et₂O: diethyl ether
EtOAc: ethyl acetate
EtOH: ethyl alcohol
MeOH: methanol
Prep HPLC: preparative high performance liquid chromatography
Prep TLC: preparative thin layer chromatography
TBAF: tetrabutylammonium fluoride
TFA: trifluoroacetic acid
THF: tetrahydrofuran

I. Preparation of Benzimidazoles:

Compounds **1-25**, **59-111**, and **138-143** are benzimidazole intermediates synthesized according to the procedures described in Scheme II.

5



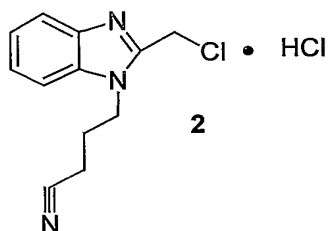
To a solution of 2-hydroxymethylbenzimidazole (29.63 g, 200 mmol) in a mixture of DMF/THF (150 mL, 1:1) was added sodium hydride (60% in mineral oil, 8.4 g, 210 mmol) in several portions at room temperature. After stirring for 1 hour, 4-bromobutyronitrile (29.6 g, 200 mmol) was added and the resulting solution was stirred at 80 °C for 16 hours. The solvent was evaporated and the residue diluted with water and extracted with EtOAc. The combined extracts were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:1 to 2:1, then EtOAc/MeOH, 10:1) to give 22.11 g (51% yield) of **1** as a white solid.

¹H NMR (CDCl₃) δ 2.27-2.32 (m, 2 H), 2.41 (t, J = 6.0 Hz, 2 H), 4.41 (t, J = 7.2 Hz, 2 H), 7.26-7.38 (m, 3 H), 7.67-7.70 (m, 1 H);
MS m/e 216 (MH⁺).

General Procedure for Converting 2-Hydroxymethyl-benzimidazoles to 2-Chloromethyl-benzimidazoles.

The procedure described below was used for the synthesis of compounds **2**, **4**, **9**, **11A+11B**, **15**, **19**, **23**, **25**, **70**, **72**, **76**, **81**, **88**, **92**, **94**, **96**, **98**, **100**, **102**, **108**, and **111** and **143**.

20



To alcohol **1** (22 g, 102.2 mmol) suspended in CH_2Cl_2 (100 mL), thionyl chloride (15.81 g, 132.9 mmol) was slowly added with ice-water bath cooling.

- 5 The ice bath was removed. The solution was stirred at room temperature for 1 hour and then evaporated. The residue was triturated with EtOAc to give a nearly quantitative yield of **2** as light gray powder.

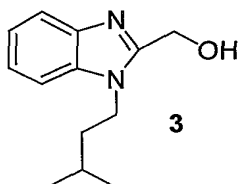
^1H NMR (CDCl_3) δ 2.32-2.38 (m, 2 H), 2.70 (t, $J = 7.3$ Hz, 2 H), 4.69 (t, $J = 7.6$ Hz, 2 H), 5.33 (s, 2 H), 7.69-7.74 (m, 2 H), 7.85-7.87 (m, 1 H), 8.00-8.02 (m, 1 H);

MS m/e 234 (MH^+).

Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_3 \cdot \text{HCl} \cdot 0.25 \text{H}_2\text{O}$: C, 52.48; H, 4.95; N, 15.30

Found: C, 52.52; H, 4.88; N, 15.26

15



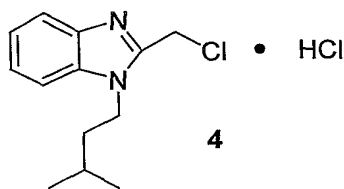
- Compound **3** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 3-methylbutylbromide.

^1H NMR (CDCl_3) δ 1.71-1.78 (m, 3 H), 4.28 (t, $J = 7.5$ Hz, 2 H), 5.02 (s, 2 H), 7.33-7.41 (m, 3 H), 7.75 (d, $J = 7.9$ Hz, 2 H);

MS m/e 219 (MH^+).

25

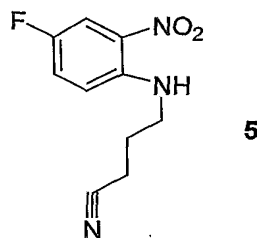
21



Compound 4 was prepared according to the same procedure described for compound 2.

5

^1H NMR (CDCl_3) δ 1.08 (d, $J = 6.4$ Hz, 6 H), 1.83-1.89 (m, 3 H), 4.57-4.60 (m, 2 H), 5.30 (s, 2 H), 7.68-7.73 (m, 2 H), 7.84-7.86 (m, 1 H), 7.93-7.95 (m, 1 H); MS m/e 237 (MH^+).

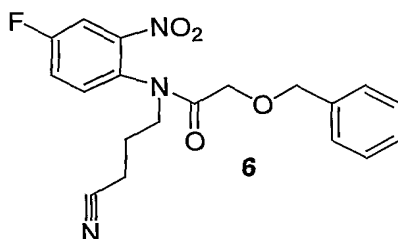


10

A solution of 2,5-difluoronitrobenzene (15.4 g, 96.8 mmol), 4-aminobutyronitrile (7.4 g, 88 mmol) and diisopropylethylamine (23 ml, 132 mmol) in DMF (250 ml) was stirred at room temperature for 32 hours. After filtration, the solvent was evaporated and the orange solid was recrystallized from MeOH (250 ml) to afford 5 (14 g, 65% yield) as orange crystals.

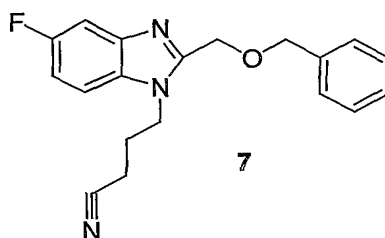
^1H NMR (CDCl_3) δ 2.06-2.12 (m, 2 H), 2.54 (t, $J = 7.0$ Hz, 2 H), 3.48-3.53 (m, 2 H), 6.85-6.88 (m, 1 H), 7.27-7.31 (m, 1 H), 7.89-7.92 (m, 1 H); MS m/e 224 (MH^+).

20



To a suspension of nitrile **5** (10.8 g, 48.4 mmol) and potassium carbonate (20.1 g, 145 mmol) in CH₃CN (200 ml) was added benzyloxyacetyl chloride (7.64 ml, 48.4 mmol) dropwise. After stirring at room temperature for 12 hours, the mixture was diluted with EtOAc (500 ml) and filtered. The filtrate was washed with 1 N HCl, brine, dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 1:1) to yield **6** (7.5 g, 42% yield) as a viscous pale yellow oil.

¹H NMR (CDCl₃) δ 1.86-1.98 (m, 2 H), 2.38-2.51 (m, 2 H), 3.34-3.39 (m, 1 H), 3.80-3.87 (m, 2 H), 4.06-4.14 (m, 1 H), 4.40-4.48 (m, 2 H), 7.18-7.19 (m, 1 H), 7.26-7.40 (m, 5 H), 7.72-7.74 (m, 1 H); MS m/e 394 (MH⁺).



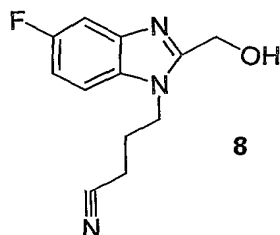
15

In a flask equipped with a mechanical stirrer, a suspension of compound **6** (6.40 g, 17.25 mmol), iron powder (2.89 g, 51.8 mmol) and ammonium chloride (4.61 g, 86.2 mmol) in a mixture of MeOH and H₂O (200 ml, 1:1) was stirred at reflux for 4 hours. The mixture was filtered through a pad of Celite and washed with MeOH. The filtrate was evaporated and the residue was taken up in EtOAc (500 ml), washed with brine, dried over MgSO₄, and evaporated. To the residue was added CH₃CN (100 ml) and acetic acid (1 ml), and the mixture was stirred at reflux for 4 hours. The solvent was evaporated and the residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 2:1) to give **7** (4.42 g, 75% yield) as a viscous oil which solidified upon standing.

25

¹H NMR (CDCl₃) δ 2.15-2.20 (m, 2 H), 2.31 (t, J = 7.0 Hz, 2 H), 4.35 (t, J = 7.2 Hz, 2 H), 4.62 (s, 2 H), 4.83 (s, 2 H), 7.07-7.11 (m, 1 H), 7.29-7.38 (m, 6 H), 7.43-7.46 (dd, J = 2.4, 9.2 Hz, 1 H);

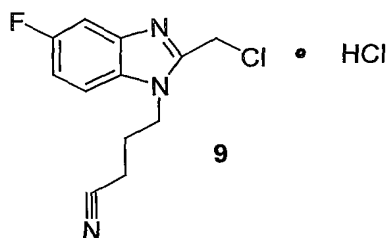
MS m/e 324 (MH⁺).



5 To a solution of **7** (3.23 g, 10 mmol) in CH₂Cl₂ (100 ml) at 0 °C was added boron tribromide (2.84 ml, 30 mmol). After stirring for 1 hour, the mixture was quenched with saturated NaHCO₃ solution with ice bath cooling and extracted with EtOAc. The combined extracts were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient,
10 CH₂Cl₂/MeOH, 40:1 to 20:1) to give **8** (1.68 g, 72% yield) as an off-white solid.

¹H NMR (CDCl₃) δ 2.25-2.30 (m, 2 H), 2.43 (t, J = 7.1 Hz, 2 H), 4.41 (t, J = 7.1 Hz, 2 H), 4.85 (s, 2 H), 7.04-7.081 (m, 1 H), 7.29-7.34 (m, 2 H);
MS m/e 234 (MH⁺).

15



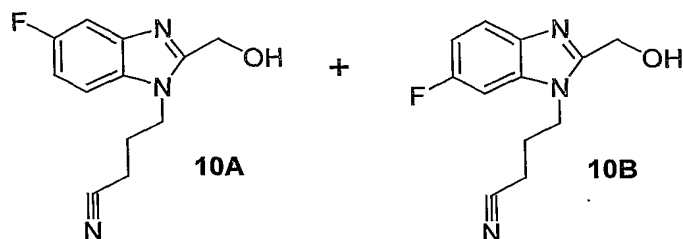
Compound **9** was prepared according to the same procedure described for compound **2**.

20

¹H NMR (CD₃OD) δ 2.30-2.36 (m, 2 H), 2.70 (t, J = 7.2 Hz, 2 H), 4.67 (t, J = 7.6 Hz, 2 H), 5.30 (s, 2 H), 7.49-7.54 (dt, J = 2.4, 9.2 Hz, 1 H), 7.62-7.64 (dd, J = 2.4, 8.0 Hz, 1 H), 8.01-8.04 (dd, J = 2.0, 9.2 Hz, 1 H);
MS m/e 252 (MH⁺).

25

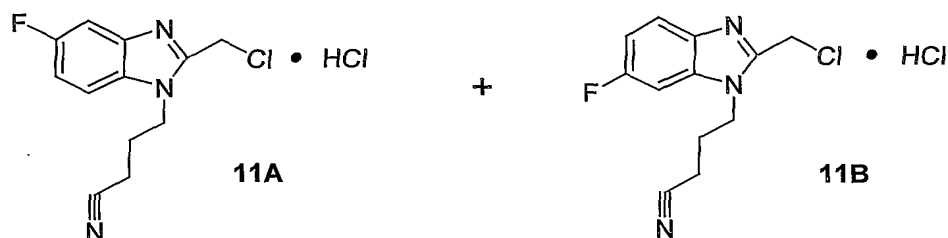
24



A mixture of **10A** and **10B** was prepared from 5-fluoro-2-hydroxymethylbenzimidazole using the same procedure described for compound **1**.

5

^1H NMR (CDCl_3) δ 2.26-2.30 (m, 2 H), 2.42-2.46 (m, 2 H), 4.36-4.42 (m, 2 H), 4.87 (s, 2 H), 7.03-7.07 (m, 1.5 H), 7.30-7.32 (m, 1 H), 7.60-7.63 (m, 0.5 H); MS m/e 234 (MH^+).

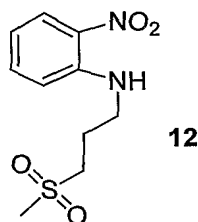


10

Compounds **11A** and **11B** were prepared according to the same procedure described for compound **2**.

15 ^1H NMR (CDCl_3) δ 2.24-2.30 (m, 2 H), 2.44-2.47 (m, 2 H), 4.32-4.39 (m, 2 H), 4.829 (s, 1 H), 4.831 (s, 1 H), 7.01-7.11 (m, 1.5 H), 7.30-7.33 (dd, $J = 4.4, 8.8$ Hz, 0.5 H), 7.40-7.42 (dd, $J = 2.3, 9.0$ Hz, 0.5 H), 7.66-7.68 (dd, $J = 4.8, 8.8$ Hz, 0.5 H); MS m/e 252 (MH^+).

20



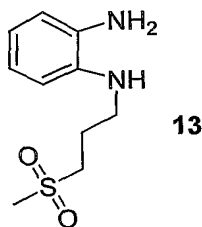
2-Fluoronitrobenzene (35.4 g, 250.9 mmol), 3-(methylthio)propylamine (24.0g, 228.1 mmol) and potassium carbonate (47.3 g, 342 mmol) were stirred in CH₃CN (100 mL) at room temperature overnight. After stirring for an additional hour at reflux, the mixture was cooled to room temperature and filtered. The
5 filtrate was evaporated. To the residue in DMF (150 mL), magnesium monoperoxyphthalate hexahydrate (MMPP, 168 g, 340 mmol) was added in several portions with ice-water cooling. The mixture was stirred at room temperature for 3 hours and the solvent was evaporated. The residue was dissolved in CH₂Cl₂ and washed with 1 N NaOH, water, brine, dried over MgSO₄
10 and evaporated. The residue was triturated with hot EtOAc to give **12** (48.7 g, 75% yield) as an orange solid.

¹H NMR (CDCl₃) δ 2.25-2.35 (m, 2 H), 2.97 (s, 3 H), 3.17 (t, J = 7.2 Hz, 2 H), 3.59 (t, J = 6.9 Hz, 2 H), 6.68 -6.74 (m, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 7.45-7.51
15 (m, 1 H), 8.20 (dd, J = 1.5, 8.7 Hz, 1 H);

MS m/e 259 (MH⁺);

Anal. Calcd for C₁₀H₁₄N₂O₄S: C, 46.50; H, 5.46; N, 10.84

Found: C, 46.53; H, 5.54; N, 10.90.

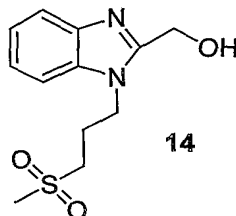


20

To a suspension of **12** (48.5 g, 187.8 mmol) in a mixture of CHCl₃ and MeOH (150 mL, 1:3) was added 10% palladium on carbon (6 g) under nitrogen. The reduction was carried out in a Parr shaker with hydrogen pressure maintained
25 between 40 and 60 psi for 25 minutes. The catalyst was removed by filtration through a pad of Celite and the filtrate was evaporated to give crude **13**.

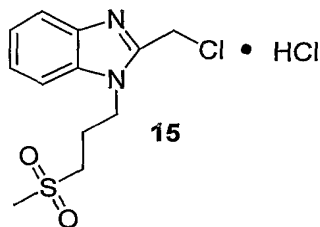
¹H NMR (CD₃OD) δ 2.11-2.21 (m, 2 H), 2.98 (s, 3 H), 3.28-3.36 (m, 4 H), 6.75 (dt, J = 0.9, 7.2 Hz, 1 H), 6.85 (d, J = 7.5 Hz, 1 H), 7.06-7.12 (m, 2 H);

MS m/e 229 (MH^+).



5 The crude diamine **13** obtained above was stirred at reflux overnight with glycolic acid (15.7 g, 207 mmol) in 6 N HCl (150 mL). The solution was cooled in an ice bath and neutralized with concentrated NH_4OH solution, extracted with EtOAc, dried over MgSO_4 and evaporated. The residue was purified by chromatography (gradient, EtOAc/hexane, 1:1 to EtOAc/MeOH, 10:1) to give a product which crystallized from EtOAc/MeOH to afford 25.7 g (51% yield in two steps) of **14**.

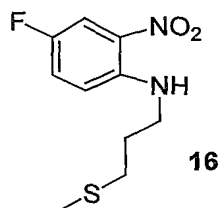
^1H NMR (CD_3OD) δ 2.38-2.44 (m, 2 H), 2.97 (s, 3 H), 3.24 (t, $J = 7.6$ Hz, 2 H), 4.54 (t, $J = 7.6$ Hz, 2 H), 7.27 (t, $J = 1.1, 8.1$ Hz, 1 H), 7.33 (dt, $J = 1.1, 8.0$ Hz, 1 H), 7.62 (d, $J = 8.1$ Hz, 1 H), 7.64 (dd, $J = 1.0, 8.0$ Hz, 1 H);
 15 MS m/e 269 (MH^+).



20 Compound **15** was prepared according to the same procedure described for compound **2**.

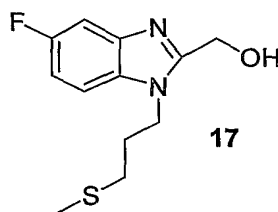
^1H NMR (CD_3OD) δ 2.46-2.52 (m, 2 H), 3.03 (s, 3 H), 3.37 (t, $J = 7.1$ Hz, 2 H), 4.77 (t, $J = 7.8$ Hz, 2 H), 5.31 (s, 2 H), 7.68-7.73 (m, 2 H), 7.86 (dd, $J = 2.8, 6.9$ Hz, 1 H), 8.03 (dd, $J = 1.7, 6.1$ Hz, 1 H);
 25

MS m/e 287 (MH^+).



To a solution of 2,5-difluoronitrobenzene (15.1 g, 95.06 mmol) in CH_3CN (150 mL) was added potassium carbonate (26.3 g, 190.11 mmol) and 3-(methylthio)propylamine (10.0 g, 95.06 mmol). The mixture was stirred vigorously with the aid of a mechanical stirrer for 16 hours at room temperature. The solid was filtered and the filtrate was evaporated. The residue was diluted with EtOAc (600 mL) and washed with water and brine. The organic layer was dried over anhydrous MgSO_4 and evaporated to give crude **16** as an orange solid (25 g, 70% pure).

^1H NMR (CDCl_3) δ 1.97-2.01 (m, 2 H), 2.11 (s, 3 H), 2.62 (t, $J = 6.9$ Hz, 2 H), 3.43 (q, $J = 6.3$ Hz, 2 H), 6.87 (dd, $J = 4.6, 9.3$ Hz, 1 H), 7.22-7.24 (m, 1 H), 7.85 (dd, $J = 3.1, 9.3$ Hz, 1 H), 7.95 (bs, 1 H);
MS m/e 245 (MH^+).



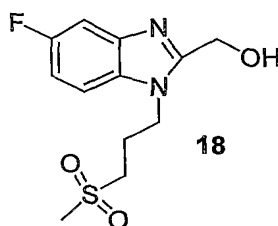
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A solution of **16** (25 g) in MeOH (300 mL) was added to a mixture of iron powder (12.0 g, 214.9 mmol) and ammonium chloride (19.2 g, 358.2 mmol) in water (100 mL). The reaction mixture was vigorously stirred with a mechanical stirrer and heated at 90 °C for 16 hours. The mixture was filtered through a plug of Celite which was rinsed with hot methanol. The solvent was evaporated to give the crude diamine. LC-MS m/e 215 (MH^+).

25

The diamine (500 mg crude, 2.33 mmol) and glycolic acid (266 mg, 3.50 mmol) were heated at reflux in 4 N hydrochloric acid (15 mL) for 16 hours. The aqueous solution was cooled and neutralized with concentrated NH_4OH (15 mL). The aqueous solution was then extracted with EtOAc. The organic extracts were dried over anhydrous MgSO_4 , filtered and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexanes, 2:1 to EtOAc/MeOH, 10:1) to give **17** (150 mg, 25% yield).

^1H NMR (CD_3OD) δ 2.08 (s, 3 H), 2.12-2.20 (m, 2 H), 2.53 (t, $J = 6.9$ Hz, 2 H), 4.43 (t, $J = 6.3$ Hz, 2 H), 4.85 (s, 2 H), 7.07 (dt, $J = 2.4, 9.2$ Hz, 1 H), 7.30 (dd, $J = 2.4, 9.3$ Hz, 1 H), 7.53 (dd, $J = 4.6, 8.9$ Hz, 1 H); MS m/e 255 (MH^+).



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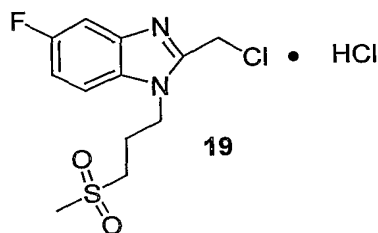
To a solution of sulfide **17** (150 mg, 0.59 mmol) in DMF (5 mL) was added magnesium monoperoxyphosphate hexahydrate (MMPP, 583 mg, 1.18 mmol). The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated, and the residue was diluted with water and extracted with EtOAc. The combined extracts were washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous MgSO_4 , filtered and evaporated. The residue was purified by flash chromatography (gradient, straight EtOAc to EtOAc/MeOH, 10:1) to give **18** (129 mg, 76% yield) as a white solid.

^1H NMR (CD_3OD) δ 2.37-2.47 (m, 2 H), 3.00 (s, 3 H), 3.26 (t, $J = 7.4$ Hz, 2 H), 4.55 (t, $J = 7.5$ Hz, 2 H), 7.14 (dt, $J = 2.4, 9.4$ Hz, 1 H), 7.34 (dd, $J = 2.4, 9.2$ Hz, 1 H), 7.62 (dd, $J = 4.5, 8.9$ Hz, 1 H); IR (KBr, cm^{-1}) 3139, 1624, 1591, 1489, 1478, 1446, 1416, 1308, 1270, 1143, 1134, 1047, 951, 859, 802, 527, 500;

MS m/e 287 (MH^+);

Anal. Calcd for $C_{12}H_{15}FN_2O_3S$: C, 50.33; H, 5.28; N, 9.78

Found: C, 50.17; H, 5.17; N, 9.57.

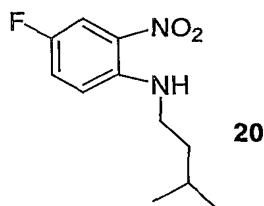


5

Compound **19** was prepared according to the same procedure described for compound **2**.

- 10 1H NMR ($DMSO-d_6$) δ 2.15-2.20 (m, 2 H), 3.00 (s, 3 H), 3.26 (t, $J = 7.2$ Hz, 2 H), 4.47 (t, $J = 7.8$ Hz, 2 H), 5.11 (s, 2 H), 7.27 (dt, $J = 2.4, 9.4$ Hz, 1 H), 7.51 (dd, $J = 2.4, 9.0$ Hz, 1 H), 7.76 (dd, $J = 4.8, 9.0$ Hz, 1 H);
IR (KBr, cm^{-1}) 3429, 2577, 1635, 1536, 1496, 1290, 1277, 1130, 962, 927, 784;
MS m/e 305 (MH^+).

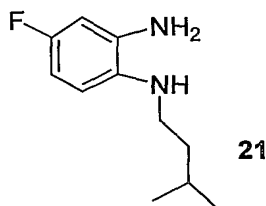
15



- To a solution of 2,5-difluoronitrobenzene (45 g, 282.86 mmol) in CH_3CN (500 mL) was added potassium carbonate (78 g, 565.72 mmol) and isoamylamine (25 g, 282.86 mmol). The reaction mixture was stirred at room temperature for 18 hours with the aid of a mechanical stirrer. The potassium carbonate was filtered and the filtrate was evaporated to give an orange oil. The oil was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by flash column chromatography (hexanes/EtOAc, 20:1) gave 53 g (83% yield) of compound **20**.

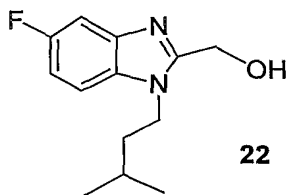
25

^1H NMR (CDCl_3) δ 0.98 (d, $J = 6.5$ Hz, 6 H), 1.61-1.65 (m, 2 H), 1.74-1.78 (m, 1 H), 3.30 (t, $J = 7.3$ Hz, 2 H), 6.83 (dd, $J = 4.6, 9.5$ Hz, 1 H), 7.23-7.27 (m, 1 H), 7.85 (dd, $J = 3.1, 9.2$ Hz, 1 H).



To a solution of compound **20** (53 g, 235.14 mmol) and concentrated HCl (15 mL) in MeOH (200 mL) was added 10% palladium on carbon (5 g) and the mixture was agitated under H_2 at 55 psi for 1.5 hours. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give 47 g (87% yield) of diamine **21** as the HCl salt.

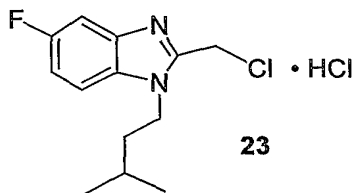
^1H NMR (CDCl_3) δ 0.97 (d, $J = 6.2$ Hz, 6 H), 1.65-1.77 (m, 3 H), 3.36 (t, $J = 8.0$ Hz, 2 H), 6.50-6.57 (m, 1 H), 6.71 (dd, $J = 2.7, 10.5$ Hz, 1 H), 7.28 (dd, $J = 5.5, 8.8$ Hz, 1 H);
MS m/e 197 (MH^+).



A mixture of diamine **21** (47 g, 200.66 mmol) and glycolic acid (16 g, 210.70 mmol) in 4 N HCl (500 mL) was stirred at reflux for 18 hours. The reaction mixture was cooled first to room temperature and then to 0°C . The reaction was diluted with concentrated ammonium hydroxide (200 mL) until the pH was adjusted to approximately 8. The product was extracted with EtOAc, dried over MgSO_4 , and evaporated. The crude product was recrystallized with EtOAc/hexanes to give 27 g (37% yield) of compound **22** as brown crystals.

^1H NMR (CDCl_3) δ 1.02 (d, $J = 6.0$ Hz, 6 H), 1.68-1.75 (m, 3 H), 3.19 (bs, 1 H), 4.22 (t, $J = 7.7$ Hz, 2 H), 4.93 (s, 2 H), 7.06 (dt, $J = 2.2, 9.1$ Hz, 1 H), 7.26-7.28 (m, 1 H), 7.37 (dd, $J = 2.1, 8.9$ Hz, 1 H);
MS m/e 237 (MH^+).

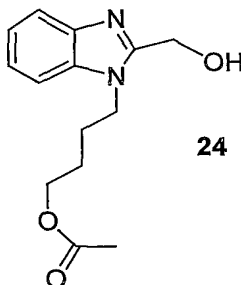
5



Compound **23** was prepared according to the same procedure described for compound **2**.

10

^1H NMR (CDCl_3) δ 1.08 (d, $J = 6.4$ Hz, 6 H), 1.79-1.90 (m, 3 H), 4.44 (bt, $J = 8.2$ Hz, 2 H), 5.32 (s, 2 H), 7.36 (dt, $J = 2.2, 8.9$, 1 H), 7.54-7.59 (m, 2 H);
MS m/e 255 (MH^+).



15

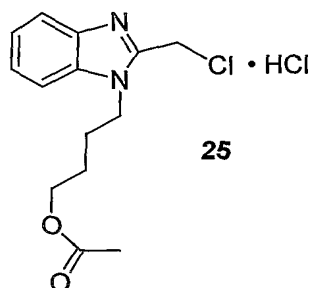
Compound **24** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 4-bromobutyl acetate.

20

^1H NMR (CDCl_3) δ 1.68-1.72 (m, 2 H), 1.91-1.94 (m, 2 H), 2.03 (s, 3 H), 4.07 (t, $J = 6.4$ Hz, 2 H), 4.26 (t, $J = 7.5$ Hz, 2 H), 4.86 (s, 2 H), 6.86 (bs, 1 H), 7.20-7.29 (m, 3 H), 7.65 (dd, $J = 1.8, 6.7$ Hz, 1 H);
MS m/e 263 (MH^+).

25

32

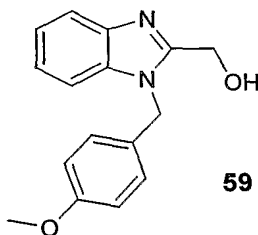


Compound **25** was prepared according to the same procedure described for compound **2**.

5

^1H NMR (CDCl_3) δ 1.80-1.86 (m, 2 H), 2.03 (s, 3 H), 2.06-2.12 (m, 2 H), 4.14 (t, $J = 6.1$ Hz, 2 H), 4.55 (t, $J = 8.1$ Hz, 2 H), 5.42 (s, 2 H), 7.48 (t, $J = 7.3$ Hz, 1 H), 7.55 (t, $J = 7.3$ Hz, 1 H), 7.64 (d, $J = 8.5$ Hz, 1 H), 7.78 (d, $J = 8.2$ Hz, 1 H); MS m/e 281 (MH^+).

10

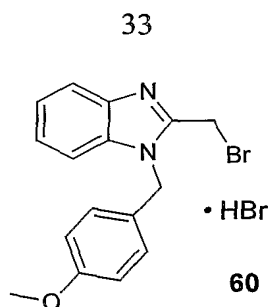


Compound **59** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 4-methoxybenzyl chloride.

15

^1H NMR (CDCl_3) δ 3.77 (s, 3 H), 4.99 (s, 2 H), 5.45 (s, 2 H), 6.84 (d, $J = 8.6$ Hz, 2 H), 7.11 (d, $J = 8.6$ Hz, 2 H), 7.28-7.34 (m, 3 H), 7.75 (d, $J = 6.8$, 1 H); MS m/e 269 (MH^+).

20



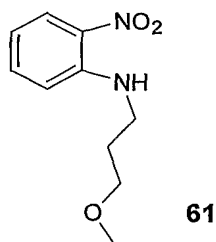
Compound **59** (4.75 g, 17.7 mmol) was combined with CH₂Cl₂ (100 mL) and the mixture was treated with (bromomethylene)dimethylammonium bromide (5.25 g, 23.0 mmol). The reaction was stirred at room temperature for 30 minutes and then filtered to isolate a white solid. The solid was rinsed with CH₂Cl₂, then with diethyl ether. The solid was triturated with water (50 mL), isolated by filtration, rinsed with water, then with acetone, and finally with Et₂O. The white powder was labeled crop 1 and set aside. All liquids were combined and concentrated in vacuo to give an off-white solid which was triturated with a mixture of acetone (50 mL) and Et₂O (300 mL). The liquid was decanted and the solid was suspended in acetone and isolated by filtration to give crop 2. Crops 1 and 2 were determined to be spectroscopically identical and were combined to give 6.65 g (91 % yield) of compound **60** as a white powder.

15

¹H NMR (DMSO-d₆) δ 3.72 (s, 3 H), 5.18 (s, 2 H), 5.68 (s, 2 H), 6.92 (d, J = 8.7 Hz, 2 H), 7.29 (d, J = 8.7 Hz, 2 H), 7.44-7.47 (m, 2 H), 7.62-7.63 (m, 1 H), 7.78-7.80 (m, 1 H);

MS m/e 332 (MH⁺).

20

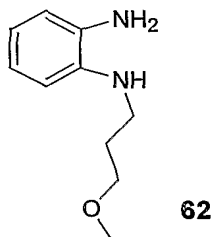


Compound **61** was prepared according to the same procedure described for compound **16** using 3-methoxypropylamine instead of 3-(methylthio)propylamine.

25

^1H NMR (CDCl_3) δ 1.95-2.00 (m, 2 H), 3.37 (s, 3 H), 3.39-3.43 (m, 2 H), 3.52 (t, $J = 5.7$ Hz, 2 H), 6.61 (t, $J = 8.2$ Hz, 1 H), 6.86 (d, $J = 8.8$ Hz, 1 H), 7.41 (t, $J = 7.9$ Hz, 1 H), 8.14 (dd, $J = 1.4, 8.7$ Hz, 1 H), 8.26 (bs, 1 H);
MS m/e 211 (MH^+).

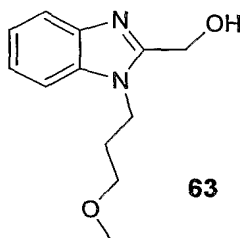
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Compound **62** was prepared from compound **61** according to the same procedure described for compound **13** and was used immediately upon isolation.

10

MS m/e 181 (MH^+).

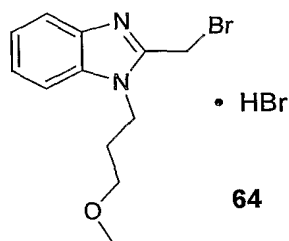


15 Compound **63** was prepared from compound **62** according to the same procedure described for compound **14**.

^1H NMR (CDCl_3) δ 2.09-2.14 (m, 2 H), 3.30 (t, $J = 5.7$ Hz, 2 H), 3.33 (s, 3 H), 4.35 (t, $J = 6.9$ Hz, 2 H), 4.89 (s, 2 H), 7.22-7.26 (m, 2 H), 7.35-7.37 (m, 1 H), 7.69-7.70 (m, 1 H);
MS m/e 221 (MH^+).

20

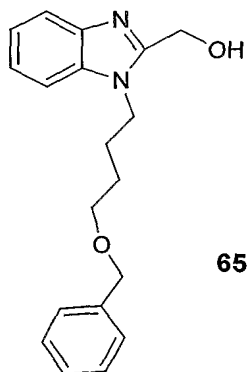
35



A solution of compound **63** (1.50 g, 6.81mmol) in CH₃CN (20 mL) was treated with (bromomethylene)dimethylammonium bromide. The reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with H₂O (3 mL) and the solvent was evaporated and dried under vacuum to give compound **64** which was used immediately upon isolation.

MS m/e 283, 285 (MH⁺).

10



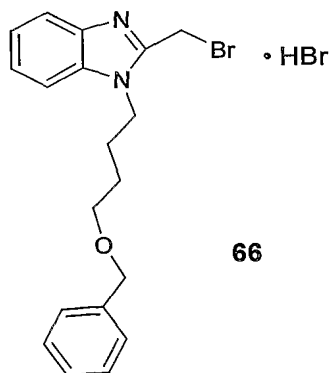
Compound **65** was prepared according to the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with benzyl 4-bromobutylether.

15

¹H NMR (CD₃OD) δ 1.65-1.71 (m, 2 H), 1.94-1.99 (m, 2 H), 3.52 (t, J = 6.2 Hz, 2 H), 4.36 (t, J = 7.7 Hz, 2 H), 4.47 (s, 2 H), 4.84 (s, 2 H), 7.22-7.27 (m, 3 H), 7.27-7.31 (m, 4 H), 7.48 (d, J = 7.4 Hz, 1 H), 7.61 (dd, J = 1.4, 7.1 Hz, 1 H);

20 MS m/e 311 (MH⁺).

36

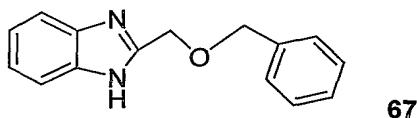


66

Compound 66 was prepared according to the same procedure described for compound 64.

5

MS m/e 373, 375 (MH⁺).

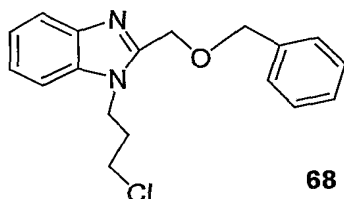


67

10 To a suspension of 1,2-phenylenediamine (50 g, 462 mmol) in THF (150 mL) cooled at 0°C was slowly added a solution of benzyloxyacetyl chloride (171 g, 924 mmol) in THF (100 mL). The reaction mixture was stirred for 3 hours. The reaction mixture was cooled to 0 °C with an ice bath and 4N HCl (300 mL) was slowly added to the reaction mixture. The ice bath was removed and the mixture was heated at reflux for 18 hours. The majority of the THF was evaporated. The aqueous material was neutralized with 10 N NaOH, extracted with EtOAc, dried over MgSO₄, and evaporated to give a tan solid. The solid was recrystallized from EtOAc to give 45 g (41% yield) of compound 67.

20 ¹H NMR (CD₃OD) δ 4.65 (s, 2 H), 4.77 (s, 2 H), 7.22-7.41 (m, 7 H), 7.56 (dd, J = 3.2, 6.1 Hz, 2 H);
MS m/e 239 (MH⁺).

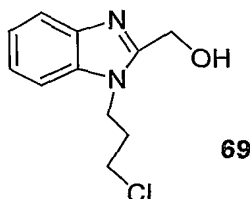
37



68

To a solution of compound **67** (6.00 g, 25.18 mmol) in DMF (50 mL) was added sodium hydride (60% dispersion in mineral oil, 1.46 g, 36.52 mmol). The reaction mixture was cooled to 0 °C and stirred for 30 minutes. To the cooled mixture 1-bromo-3-chloropropane (5.35 g, 32.99 mmol) was added and the reaction mixture was stirred for 4.5 hours. The mixture was diluted with H₂O (75 mL) and extracted with Et₂O (3 x 300 mL). The combined organic extracts were dried over MgSO₄ and evaporated. Purification by flash column chromatography on silica (gradient, hexanes/EtOAc 2:1 to 1:1) gave 6.86 g (87% yield) of compound **68**.

¹H NMR (CDCl₃) δ 2.22-2.36 (m, 2 H), 3.53 (t, J = 6.0 Hz, 2 H), 4.45 (t, J = 7.0 Hz, 2 H), 4.62 (s, 2 H), 4.90 (s, 2 H), 7.28-7.44 (m, 7 H), 7.42-7.48 (m, 1 H), 7.79-7.82 (m, 1 H); MS m/e 315, 317 (MH⁺).



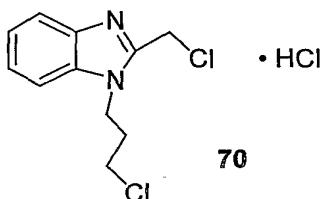
69

A solution of compound **68** (4.00 g, 12.71 mmol) in CH₂Cl₂ (75 mL) was cooled to 0 °C with an ice bath. To this solution was added boron tribromide (0.99M in CH₂Cl₂, 20 mL, 19.76 mmol) slowly via syringe. The reaction mixture was stirred at 0 °C for 2 hours. The reaction was quenched at 0 °C with MeOH (75 mL). The solvent was evaporated with a room temperature rotary evaporator bath. More MeOH was added and was again evaporated. The resulting solid was dried under high vacuum for 48 hours to give 3.70 g (95% yield) of compound **69**.

^1H NMR (CD_3OD) δ 2.39-2.44 (m, 2 H), 3.72 (t, $J = 6.0$ Hz, 2 H), 4.61 (t, $J = 7.2$ Hz, 2 H), 5.19 (s, 2 H), 7.62-7.68 (m, 2 H), 7.80-7.82 (m, 1 H), 7.93-7.95 (m, 1 H);

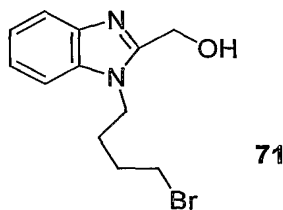
MS m/e 225, 227 (MH^+).

5



Compound 70 was prepared according to the same procedure described for compound 2.

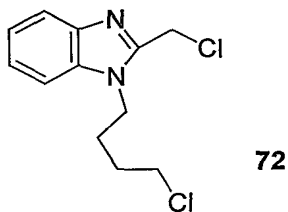
10 MS m/e 244 (MH^+).



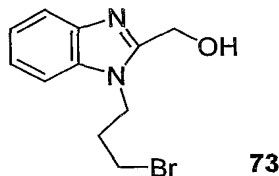
15 Compound 71 was prepared according to the same procedure described for compound 1 using 1,4-dibromobutane and the reaction was carried out at 0 °C.

^1H NMR (CD_3OD) δ 1.91-1.95 (m, 2 H), 2.01-2.08 (m, 2 H), 3.48 (t, $J=6.6$ Hz, 2 H), 4.38 (t, $J=7.4$ Hz, 2 H), 4.86 (s, 2 H), 7.23-7.27 (m, 1 H), 7.29-7.32 (m, 1H), 7.54 (d, $J=8.0$ Hz, 1 H), 7.62 (d, $J=8.0$ Hz, 1 H);

20 MS m/e 282, 284 (MH^+).



Compound **72** was prepared according to the same procedure described for compound **2** and was used immediately upon isolation.

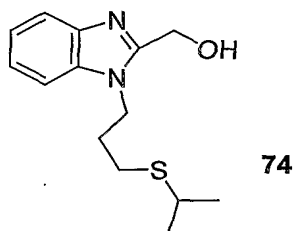


5

Compound **73** was prepared according to the same procedure described for compound **1** using 1,3 dibromopropane and the reaction was carried out at 0 °C.

¹H NMR (CDCl₃) δ 2.42-2.47 (m, 2 H), 3.43 (t, J= 6.1 Hz, 2 H), 4.43 (t, J=7.0 Hz, 2 H), 4.94 (s, 2 H), 7.25-7.32 (m, 2 H), 7.42-7.44 (m, 1 H), 7.68-7.70 (m, 1 H);
MS m/e 268, 270 (MH⁺).

10



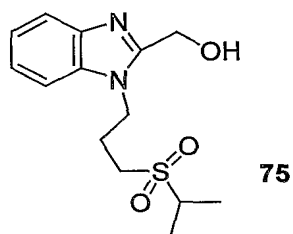
2-Propanethiol (305 mg, 4.00 mmol) and sodium hydride (60% dispersion in mineral oil, 240 mg, 6.00 mmol) were stirred together in DMF (20 mL) and then cooled to 0 °C. To this mixture was added compound **73** (542 mg, 2.00 mmol) and the reaction mixture was allowed to warm to room temperature over 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over MgSO₄, and evaporated. Purification by column chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) gave 310 mg (59% yield) of compound **74** as an off-white oil.

15

20

^1H NMR (CD_3OD) δ 1.22 (d, $J = 6.7$ Hz, 6 H), 2.10-2.18 (m, 2 H), 2.58 (t, $J=7.0$ Hz, 2 H), 2.90-2.93 (m, 1 H), 4.45 (t, $J=7.3$ Hz, 2 H), 4.87 (s, 2 H), 7.23-7.32 (m, 2 H), 7.55 (d, $J=8.0$ Hz, 1 H), 7.62 (d, $J=7.9$ Hz, 1 H);

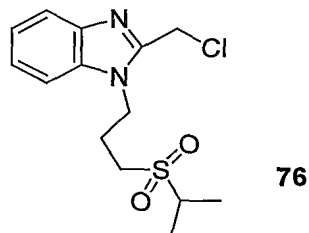
5 MS m/e 265 (MH^+).



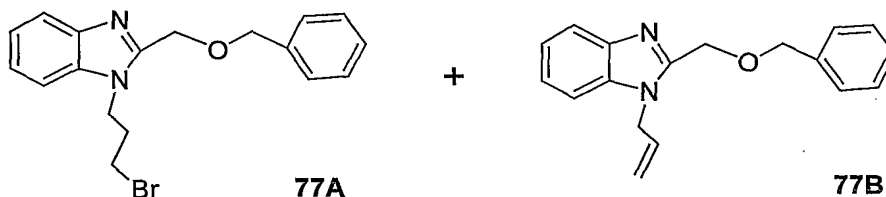
10 Compound 75 was prepared from compound 74 according to the same procedure described for compound 18.

^1H NMR (CD_3Cl) δ 1.32-1.36 (m, 6 H), 2.44-2.50 (m, 2 H), 3.00-3.02 (m, 2 H), 3.06-3.10 (m, 1 H), 4.48 (t, $J=7.3$ Hz, 2 H), 4.87 (s, 2 H), 7.23-7.30 (m, 2 H), 7.42 (d, $J=7.7$ Hz, 1 H), 7.65 (d, $J=7.8$ Hz, 1 H);

15 MS m/e 297 (MH^+).



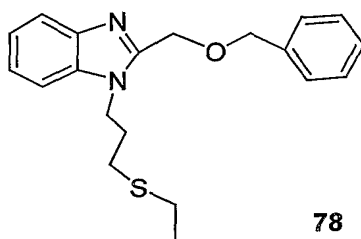
20 Compound 76 was prepared according to the same procedure described for compound 2 and was used immediately upon isolation.



To a solution of compound **67** (18.25 g, 76.59 mmol) in DMF (85 mL) was added sodium hydride (60% dispersion in mineral oil, 3.37 g, 84.25 mmol). The reaction mixture was stirred for 30 minutes and then cooled to 0 °C. 1,3-Dibromopropane was slowly added to the cooled solution. The temperature was raised to room temperature after 20 minutes as no starting material remained. The reaction mixture was diluted with H₂O and extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and evaporated. Column chromatography (hexanes/EtOAc, 2:1) gave 5.2 g of a 60/40 mixture of the desired bromide compound **77A** (8% yield) and an undesired elimination product **77B**. This mixture was used in the next step without further purification.

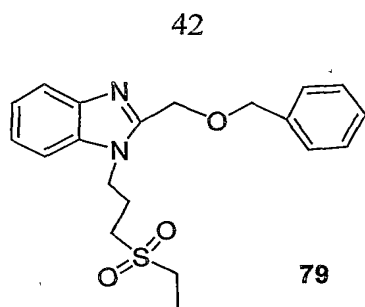
Bromide **77A** : MS m/e 360,361 (MH⁺);

Elimination product **77B** : MS m/e 279 (MH⁺).



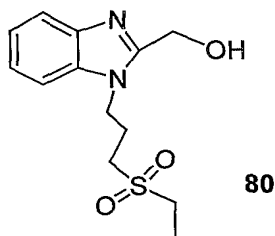
15

To a solution of ethanethiol (1.04 g, 16.77 mmol) in DMF (60 mL) was added sodium hydride (60% dispersion in mineral oil, 670 mg, 16.77 mmol). The mixture was stirred for 15 minutes at room temperature and then cooled to 0 °C. In a separate flask, the mixture containing compounds **77A** and **77B** (5.2 g mixture, 3.0 g, 8.38 mmol) was dissolved in DMF (10 mL), cooled to 0 °C and added slowly to the ethanethiol mixture. The reaction mixture was stirred for 1 hour while the temperature was slowly allowed to rise to room temperature. The DMF was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with H₂O. The organic layer was dried over MgSO₄ and evaporated. This material containing compound **78** was used immediately as a mixture without further purification.



Compound **79** was prepared from crude **78** according to the same procedure as compound **18** and was purified by flash column chromatography on silica (gradient, EtOAc/hexanes, 2:1 to straight EtOAc).

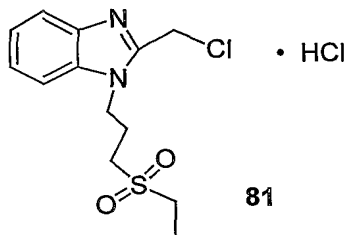
^1H NMR (CDCl_3) δ 1.21 (t, $J = 7.5$ Hz, 3 H), 2.35-2.42 (m, 2 H), 2.73 (q, $J = 7.5$ Hz, 2 H), 2.84-2.88 (m, 2 H), 4.43 (t, $J = 7.2$ Hz, 2 H), 4.60 (s, 2 H), 4.87 (s, 2 H), 7.27-7.34 (m, 5 H), 7.42 (dd, $J = 1.5, 7.0$ Hz, 1 H), 7.77 (dd, $J = 1.6, 6.9$ Hz, 1 H), 8.00 (s, 2 H);
MS m/e 373 (MH^+).



A solution of compound **79** (1.95 g, 5.24 mmol) in CH_2Cl_2 (50 mL) was cooled to 0°C with an ice bath. To this solution was added boron tribromide (0.99 M in CH_2Cl_2 , 9.0 mL, 9.00 mmol) slowly via syringe. The reaction mixture was stirred for 40 minutes at 0°C before quenching at 0°C by cautious addition of anhydrous MeOH (50 mL). The solvent was evaporated with a room temperature rotary evaporator bath. More anhydrous MeOH was added and the solvent was again evaporated. The resulting solid was dried under high vacuum for 48 hours to give 1.82 g (96% yield) of compound **80**.

^1H NMR (DMSO- d_6) δ 1.22 (t, J = 7.4 Hz, 3 H), 2.23-2.89 (m, 2 H), 3.11 (q, J = 7.4 Hz, 2 H), 3.29 (t, J = 7.7 Hz, 2 H), 4.53 (t, J = 7.5 Hz, 2 H), 5.08 (s, 2 H), 7.58-7.65 (m, 2 H), 7.80 (dd, J = 1.0, 7.3 Hz, 1 H), 8.04 (d, J = 7.75 Hz, 1 H); MS m/e 283 (MH^+).

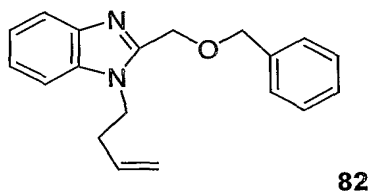
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Compound **81** was prepared according to the same procedure described for compound **2**.

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MS m/e 301 (MH^+).

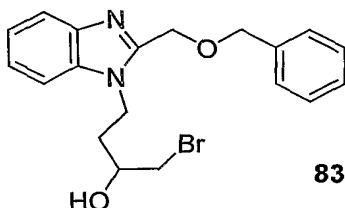


15 To a solution of compound **67** (1.43 g, 6.00 mmol) in DMF (25 mL) was added sodium hydride (60% dispersion in mineral oil, 260 mg, 6.60 mmol) and the mixture was cooled to 0 °C. To the mixture was added 4-bromo-1-butene (972 mg, 7.20 mmol) and the mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was quenched with H_2O and extracted with
20 EtOAc. The organic extracts were washed with water and then brine, dried over MgSO_4 , and evaporated. Flash column chromatography (gradient, hexanes /EtOAc, 4:1 to 1:1) gave 580 mg (33% yield) of compound **82** as a viscous oil.

^1H NMR (CDCl_3) δ 2.55-2.59 (m, 2 H), 4.31 (t, J =7.5 Hz, 2 H), 4.59 (s, 2 H), 4.88 (s, 2 H), 5.01 (d, J =7.8 Hz, 1 H), 5.04 (d, J =10.4 Hz, 1 H), 5.71-5.80 (m, 1 H), 7.26-7.39 (m, 8 H), 7.79 (d, J =7.6 Hz, 1 H);

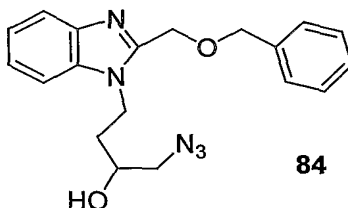
25

MS m/e 293 (MH^+).



5 To a solution of compound **82** (468 mg, 1.92 mmol) and water (71 mg, 3.93 mmol) in DMSO (5 mL) was added N-bromosuccinimide (NBS, 700 mg, 3.93 mmol) at room temperature and the mixture was stirred for 1 hour. The resulting solution was diluted with EtOAc and washed with H₂O. The organic extracts were dried with MgSO₄ and evaporated. The residue was purified by
10 flash chromatography (gradient, hexane:EtOAc 3:1 to 1:2) to give 214 mg (56% yield) of compound **83** as a off-white viscous oil.

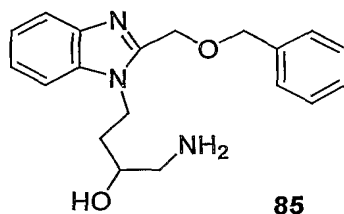
¹H NMR (CDCl₃) δ 1.90-1.97 (m, 1 H), 2.12-2.18 (m, 1 H), 3.22-3.30 (m, 2 H), 3.61-3.66 (m, 1 H), 4.38-4.50 (m, 2 H), 4.59-4.64 (m, 2 H), 4.87-4.92 (m, 2 H),
15 7.28-7.37 (m, 7 H), 7.42-7.46 (m, 1 H), 7.78-7.80 (m, 1 H);
MS m/e 389, 391 (MH^+).



20 A mixture of compound **83** (214 mg, 0.55 mmol) and sodium azide (107 mg, 1.65 mmol) in DMF (5 mL) was stirred at 50 °C for 1 hour. The resulting solution was diluted with EtOAc and washed with water. The organic extracts were dried with MgSO₄ and evaporated to give 190 mg (98% yield) of compound
84 as a off-white viscous oil.

^1H NMR (CDCl_3) δ 1.84-1.91 (m, 1 H), 2.02-2.09 (m, 1 H), 3.08-3.14 (m, 2 H), 3.52-3.56 (m, 1 H), 4.36-4.41 (m, 1 H), 4.44-4.50 (m, 1 H), 4.60-4.67 (m, 2 H), 4.88-4.93 (m, 2 H), 7.26-7.38 (m, 7 H), 7.42-7.44 (m, 1 H), 7.79-7.81 (m, 1 H); MS m/e 352 (MH^+).

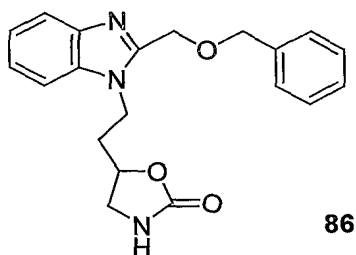
5



Compound **85** was prepared from compound **84** according to the same reduction procedure described for compound **13**.

10

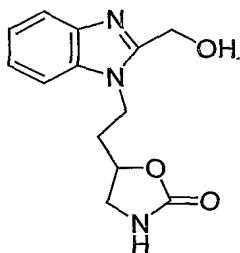
^1H NMR (CD_3OD) δ 1.86-1.94 (m, 1 H), 2.03-2.10 (m, 1 H), 2.70-2.74 (m, $J=3.2$, 12.8 Hz, 1 H), 2.84-2.88 (dd, $J=3.2$, 12.8 Hz, 1 H), 3.70-3.75 (m, 1 H), 4.44-4.54 (m, 2 H), 4.60-4.65 (m, 2 H), 4.88-4.93 (m, 2 H), 7.27-7.38 (m, 7 H), 7.59 (d, $J=8.0$ Hz, 1 H), 7.65 (d, $J=8.0$ Hz, 1 H);

15 MS m/e 326 (MH^+).

A solution of compound **85** (162 mg, 0.50 mmol), carbonyldiimidazole (89 mg, 0.55 mmol) and pyridine (198 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 2 hours. The mixture was diluted with CH_2Cl_2 and washed with water. The organic extracts were dried over MgSO_4 and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2 :MeOH, 40:1 to 20:1) to give 130 mg (74% yield) of compound **86** as a off-white viscous oil.

^1H NMR (CD_3OD) δ 2.16-2.21 (m, 2 H), 3.06-3.09 (m, 1 H), 3.52-3.59 (m, 1 H), 4.41-4.50 (m, 2 H), 4.58-4.65 (m, 3 H), 4.80-4.84 (m, 2 H), 7.26-7.38 (m, 6 H), 7.55-7.58 (m, 1 H), 7.82-7.85 (m, 1 H), 8.51-8.53 (m, 1 H); MS m/e 352 (MH^+).

5

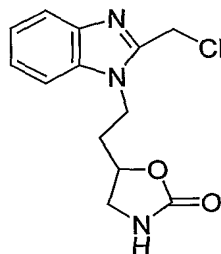


87

Compound **86** (130 mg, 0.37 mmol), palladium hydroxide on carbon (Pearlman's catalyst, 50 mg), EtOH (2 mL) and cyclohexene (1 mL) were stirred at reflux for 1 hour. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and purified by flash column chromatography (gradient, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 30:1 to 10:1) to give 20 mg (21% yield) of compound **87** as a viscous white oil.

^1H NMR (CD_3OD) δ 2.26-2.33 (m, 2 H), 3.21-3.24 (m, 1 H), 3.65 (t, $J=8.8$ Hz, 1 H), 4.50-4.54 (m, 2 H), 4.67-4.70 (m, 1 H), 4.89-4.92 (m, 2 H), 7.24-7.34 (m, 2 H), 7.57 (d, $J=8.0$ Hz, 1 H), 7.63 (d, $J=7.9$ Hz, 1 H); MS m/e 294 (MH^+).

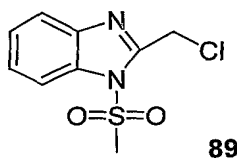
20



88

Compound **88** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

47



To a solution of 2-(chloromethyl)benzimidazole (80 g, 0.48 mol) and methanesulfonyl chloride (58.3 mL, 0.75 mol) in CH_2Cl_2 (0.5 L), triethylamine
5 (136 mL, 0.97 mol) was added dropwise under nitrogen. The resulting mixture was stirred at room temperature for 6 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated with MeOH and filtered to afford 74.9 g (64% yield) of compound **89** as a brown solid.

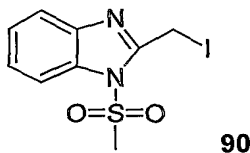
10 ^1H NMR (CDCl_3) δ 3.44 (s, 3 H), 5.11 (s, 2 H), 7.40-7.49 (m, 2 H), 7.76-7.82 (m, 1 H), 7.85-7.91 (m, 1 H);

IR (KBr, cm^{-1}) 3027, 2920, 1371, 1349, 1177, 1144, 1059;

MS m/e 245 (MH^+);

Anal. Calcd for $\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 44.18; H, 3.71; N, 11.45

15 Found: C, 44.09; H, 3.57; N, 11.49.



A solution of potassium iodide (206 g, 1.24 mol) and compound **89** (74.8
20 g, 0.414 mol) in acetone (1 L) was stirred at reflux under nitrogen for 4 hours. The solid was filtered and the filtrate was evaporated. The crude product was triturated in MeOH and filtered to give 83 g (60% yield) of compound **90** as a solid.

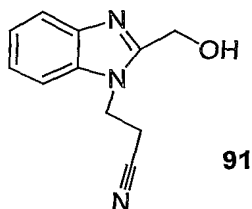
25 ^1H NMR (CDCl_3) δ 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);

IR (KBr, cm^{-1}) 3022, 2916, 1366, 1173, 1055, 966, 763, 745;

MS m/e 336 (MH^+);

Anal. Calcd for $C_9H_9IN_2O_2S$: C, 32.16; H, 2.70; N, 8.33

Found: C, 32.05; H, 2.63; N, 8.22.



5

Compound **91** was prepared according to the Michael addition procedure described by Popov, I. I. in *Khim Geterotskl. Soedin.* **1996**, 6, 781-792.

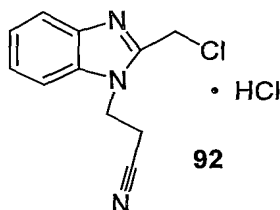
1H NMR ($CDCl_3$) δ 3.08 (t, $J = 6.8$ Hz, 2 H), 4.63 (t, $J = 6.8$ Hz, 2 H), 4.77 (d, $J = 5.7$ Hz, 2 H), 5.73 (t, $J = 5.7$ Hz, 1 H), 7.17-7.28 (m, 2 H), 7.64 (d, $J = 1.2$ Hz, 1 H), 7.70 (d, $J = 1.2$ Hz, 1 H);

MS m/e 202 (MH^+);

Anal. Calcd for $C_{11}H_{11}N_3O$: C 65.66; H, 5.51; N, 20.88

Found: C, 65.94; H, 5.57; N, 21.08.

15



Compound **92** was prepared according to the same procedure described for compound **2**.

20

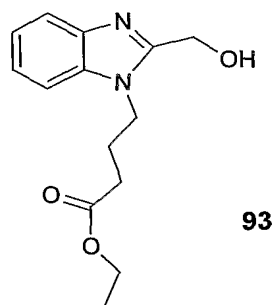
1H NMR ($CDCl_3$) δ 3.02 (t, $J = 7.0$ Hz, 2 H), 4.65 (t, $J = 7.0$ Hz, 2 H), 4.99 (s, 2 H), 7.34-7.44 (m, 3 H), 7.79-7.82 (m, 1 H);

MS m/e 220 (MH^+);

Anal. Calcd for $C_{11}H_{10}ClN_3$: C, 60.09; H, 4.65; N, 19.13

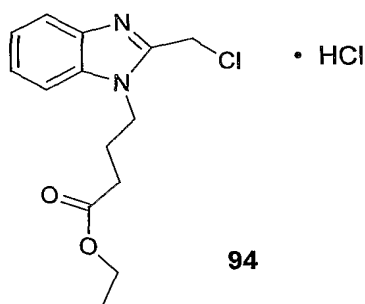
25

Found: C, 60.09; H, 4.65; N, 19.11.

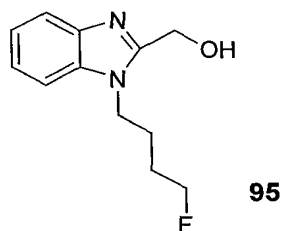


Compound **93** was prepared according to the same procedure described for
5 compound **1** except that 4-bromobutyronitrile was replaced with ethyl 4-
bromobutyrate.

^1H NMR (CDCl_3) δ 1.24 (t, $J = 7.0$ Hz, 3 H), 2.15-2.22 (m, 2 H), 2.38-2.42 (m, 2
H), 4.12 (q, $J = 7.1$ Hz, 2 H), 4.29-4.34 (m, 2 H), 4.96 (s, 2 H), 7.22-7.30 (m, 2
10 H), 7.38-7.43 (m, 1 H), 7.66-7.70 (m, 1 H);
MS m/e 250 (MH^+).



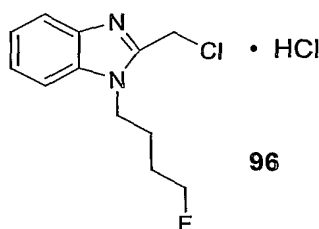
15 Compound **94** was prepared according to the same procedure described for
chloride **2** and was used immediately upon isolation.



Compound **95** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 1-bromo-4-fluorobutane.

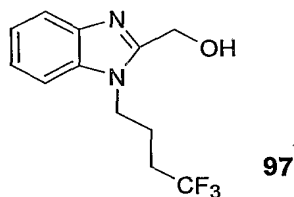
- 5 ^1H NMR (DMSO-d_6) δ 1.65-1.75 (m, 2 H), 1.85-1.90 (m, 2 H), 4.32 (t, $J = 7.5$ Hz, 2 H), 4.41 (t, $J = 6.0$ Hz, 1 H), 4.51 (t, $J = 6.0$ Hz, 1H), 4.71 (d, $J = 5.8$ Hz, 2 H), 5.62 (t, $J = 5.8$ Hz, 1 H), 7.18 (t, $J = 7.0$ Hz, 1 H), 7.23 (t, $J = 6.3$ Hz, 1 H), 7.56-7.60 (m, 2 H);
MS m/e 222 (MH^+).

10



Compound **96** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

15



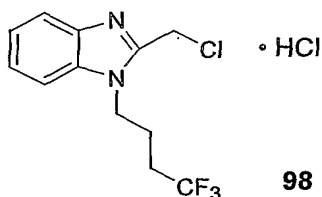
Compound **97** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 1-bromo-4,4,4-trifluorobutane.

20

^1H NMR (DMSO-d_6) δ 1.99-2.05 (m, 2 H), 2.34-2.40 (m, 2 H), 4.35-4.38 (m, 2 H), 4.73 (s, 2 H), 7.20 (t, $J = 7.2$ Hz, 1 H), 7.26 (t, $J = 7.4$ Hz, 1 H), 7.60-7.63 (m, 1 H), 7.96 (s, 1 H);

25 MS m/e 258 (MH^+).

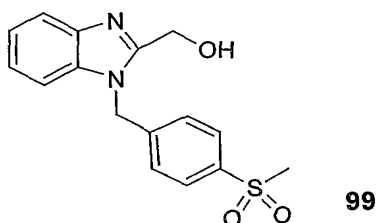
51



98

Compound 98 was prepared according to the same procedure described for chloride 2 and was used immediately upon isolation.

5



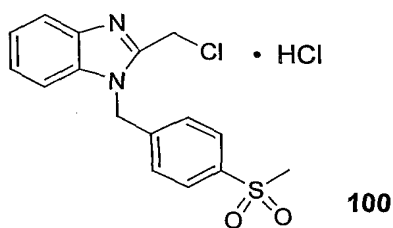
99

Compound 99 was prepared according to the same procedure described for compound 1 except that 4-bromobutyronitrile was replaced with 4-methylsulfonylbenzyl bromide.

10

^1H NMR (DMSO- d_6) δ 3.16 (s, 3 H), 4.75 (d, J = 5.6 Hz, 2 H), 5.70 (s, 2 H), 5.73-5.75 (m, 1 H), 7.17-7.21 (m, 2 H), 7.36-7.38 (m, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.64-7.65 (m, 1 H), 7.87 (d, J = 8.2 Hz, 1 H);

15 MS m/e 316 (MH^+).

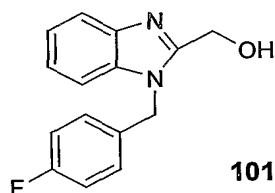


100

Compound 100 was prepared according to the same procedure described for chloride 2 and was used immediately upon isolation.

20

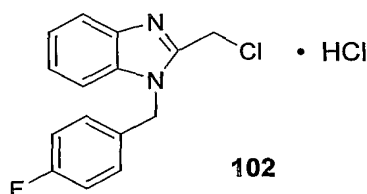
52



Compound **101** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 4-fluorobenzyl bromide.

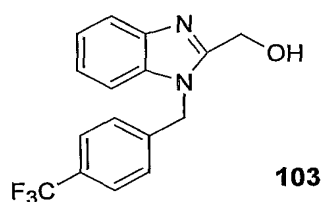
^1H NMR (DMSO- d_6) δ 4.74 (s, 2 H), 5.55 (s, 2 H), 7.13-7.18 (m, 3 H), 7.28-7.30 (m, 2 H), 7.38-7.40 (m, 1 H), 7.59-7.63 (m, 1 H);
MS m/e 256 (MH^+).

10



Compound **102** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

15

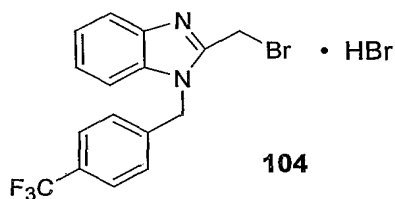


Compound **103** was prepared according to the same procedure as compound **1** except that 4-bromobutyronitrile was replaced with 4-trifluoromethylbenzyl bromide.

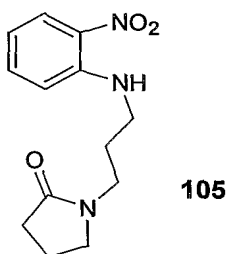
20

^1H NMR (DMSO- d_6) δ 4.74 (s, 2 H), 5.68 (s, 2 H), 7.11-7.20 (m, 2 H), 7.35-7.39 (m, 2 H), 7.62-7.64 (m, 1 H), 7.64-7.72 (m, 2 H);

MS m/e 369 (MH^+).



- 5 Compound **104** was prepared according to the same procedure described for compound **64** and was used immediately upon isolation.



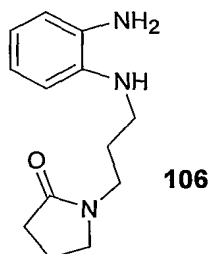
- 10 Compound **105** was prepared according to the same procedure described for compound **16** using 1-(3-aminopropyl)-2-pyrrolidinone instead of 3-(methylthio)propylamine.

1H NMR ($CDCl_3$) δ 1.93 (m, 2 H), 2.02-2.07 (m, 2 H), 2.39 (t, $J = 8.05$ Hz, 2 H),
 15 3.32-3.36 (m, 2H), 3.36-3.45 (m, 4 H), 6.64 (t, $J = 7.0$ Hz, 1 H), 6.83 (d, $J = 8.7$ Hz, 1 H), 7.42 (t, $J = 8.7$ Hz, 1 H), 8.07 (bs, 1 H), 8.16 (d, $J = 7.0$ Hz, 1 H);
 MS m/e 263 (MH^+);

Anal. Calcd for $C_{13}H_{17}N_3O_3 \cdot 0.24 H_2O$: C, 58.34; H, 6.58; N, 15.70

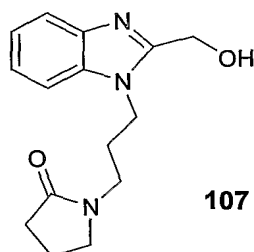
Found: C, 58.05; H, 6.20; N, 11.41.

20



Compound **106** was prepared according to the same reduction procedure described for compound **13**.

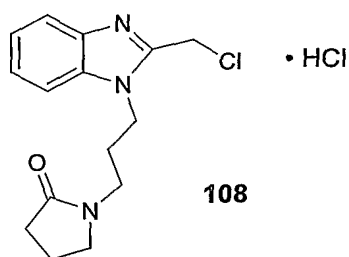
¹H NMR (CDCl₃) δ 1.83-1.88 (m, 2 H), 1.99-2.05 (m, 2 H), 2.41 (t, J = 8.0 Hz, 2 H), 3.16 (t, J = 6.5 Hz, 2 H), 3.33-3.43 (m, 4 H), 6.63-6.65 (m, 2 H), 6.70 (d, J = 7.1 Hz, 1 H), 6.78 (t, J = 7.5 Hz, 1 H), 7.26 (s, 1 H);
MS m/e 233 (MH⁺).



10

Compound **107** was prepared according to the same procedure described for compound **14**.

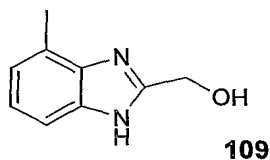
¹H NMR (DMSO-d₆) δ 1.87-1.92 (m, 2 H), 1.95-2.00 (m, 2 H), 2.21 (t, J = 8.0 Hz, 2 H), 3.25-3.34 (m, 4 H), 4.26 (t, J = 7.6 Hz, 2 H), 4.72 (s, 2 H), 5.65 (bs, 2 H);
MS m/e 273 (MH⁺).



20

Compound **108** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

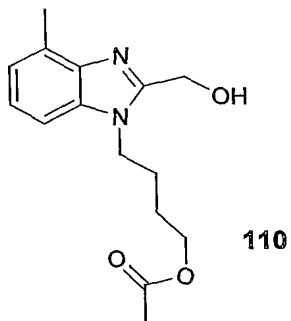
55



A mixture of 2,3-diaminotoluene (10.21 g, 83.57 mmol) and glycolic acid (9.53 g, 125.36 mmol) in 6 N HCl (100 mL) were stirred at 100 °C for 14 hours.

- 5 The reaction mixture was cooled and made basic (pH 7-8) with ammonium hydroxide. A dark brown solid was collected by filtration, washed with H₂O, and dried to give 12.47 g (92% yield) of compound **109**.

¹H NMR (DMSO-d₆) δ 2.50 (s, 3 H), 4.70 (s, 2 H), 6.93 (d, J = 7.3 Hz, 1 H), 7.04
10 (t, J = 7.6 Hz, 1 H), 7.31 (d, J = 7.9 Hz, 1 H).

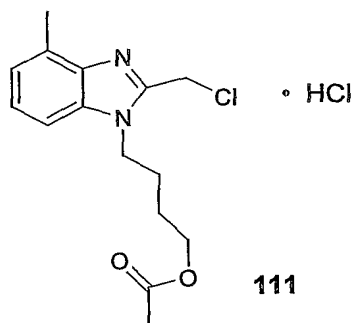


- Compound **110** was prepared according to the same procedure described
15 for compound **24** except that the base employed was cesium carbonate.

¹H NMR (CDCl₃) δ 1.67-1.73 (m, 2 H), 1.89-1.96 (m, 2 H), 2.02 (s, 3 H), 2.59 (s,
3 H), 4.05-4.10 (m, 2 H), 4.27 (t, J = 7.5 Hz, 2 H), 4.89 (s, 2 H), 7.01-7.03 (m, 1
H), 7.12-7.15 (m, 2 H);

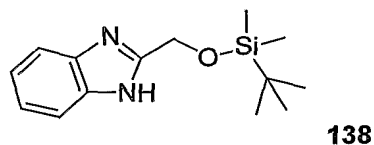
20 MS m/e 277 (MH⁺).

56



Compound 111 was prepared according to the same procedure described for chloride 2 and was used immediately upon isolation.

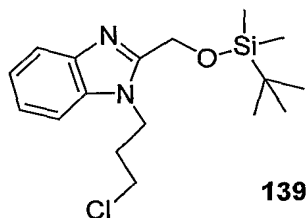
5 MS m/e 295 (MH⁺).



To a solution of 2-hydroxymethylbenzimidazole (5.92 g, 40.0 mmol) and
10 imidazole (6.81 g, 100.0 mmol) in THF (100 mL) was added *t*-butyldimethylsilyl
chloride (12.65 g, 84.0 mmol) in several portions. The resulting mixture was
stirred at room temperature for 2 hours and filtered. The filtrate was diluted with
EtOAc and washed with H₂O and brine. The organic layer was dried over MgSO₄
and evaporated. The residue was recrystallized from hexanes/EtOAc to give 8.50
15 g (81%) of compound 138 as white needles.

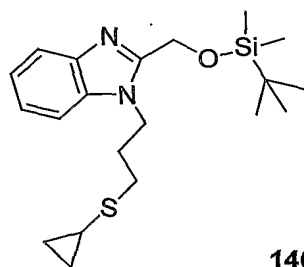
¹H NMR (CDCl₃) δ 0.15-0.16 (m, 6 H), 0.95-0.97 (m, 9 H), 5.02-5.03 (m, 2 H),
7.24-7.27 (m, 2 H), 7.59 (bs, 2 H);
MS m/e 263 (MH⁺).

20



Compound **139** was prepared according to the same procedure described for compound **68** except that cesium carbonate was used instead of sodium hydride as the base.

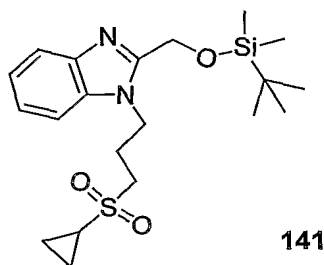
- 5 ^1H NMR (CDCl_3) δ 0.13-0.14 (m, 6 H), 0.91-0.92 (m, 9 H), 2.35-2.37 (m, 2 H), 3.58 (t, $J = 6.0$ Hz, 2 H), 4.50 (t, $J = 7.0$ Hz, 2 H), 5.01 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, $J = 8.0$ Hz, 1 H), 7.77 (d, $J = 10.0$ Hz, 1 H);
MS m/e 339 (MH^+).



- Compound **140** was prepared through the coupling of compound **139** and cyclopropylsulfide according to the same procedure described for compound **74** except using cesium carbonate instead of sodium hydride as the base. The
15 cyclopropylsulfide was prepared according to a literature procedure by E. Block, A. Schwan, and D. Dixon in *Journal of the American Chemical Society*, **1992**, *114*, 3492-3499.

- ^1H NMR (CDCl_3) δ 0.12-0.13 (m, 6 H), 0.54-0.56 (m, 2 H), 0.84-0.86 (m, 2 H),
20 0.90-0.91 (m, 9 H), 1.87-1.92 (m, 1 H), 2.20-2.25 (m, 2 H), 2.62 (t, $J = 7.0$ Hz, 2 H), 4.43 (t, $J = 7.4$ Hz, 2 H), 5.00 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, $J = 8.0$ Hz, 1 H), 7.77 (d, $J = 10.0$ Hz, 1 H);
MS m/e 377 (MH^+).

58

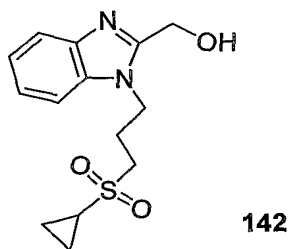


Compound **141** was prepared from compound **140** by the same procedure described for compound **18**.

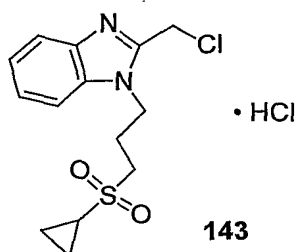
5

^1H NMR (CDCl_3) δ 0.13-0.14 (m, 6 H), 0.91-0.92 (m, 9 H), 1.01-1.03 (m, 2 H), 1.23-1.24 (m, 2 H), 2.31-2.34 (m, 1 H), 2.48-2.52 (m, 2 H), 3.07 (t, $J = 7.2$ Hz, 2 H), 4.51 (t, $J = 7.1$ Hz, 2 H), 5.00 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, $J = 8.0$ Hz, 1 H), 7.77 (d, $J = 10.0$ Hz, 1 H);

10 MS m/e 409 (MH^+).



To solution of compound **141** (27 mg, 0.07 mmol) in THF (0.5 mL) was added TBAF (1 M THF solution, 0.13 mL, 0.13 mmol) at 0°C and the mixture was stirred for 10 minutes. The solvent was evaporated and the residue was passed through a short plug of silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1) to give crude compound **142** which was used immediately upon isolation.

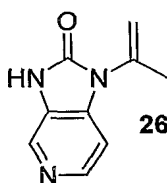


20

Compound **143** was prepared according to the same procedure described for compound **2** and was used immediately upon isolation.

II. Preparation of 2-Oxo-imidazopyridines and 2-Oxo-imidazopyrimidines:

Compounds **26-58** and **112-126** are intermediates prepared according to the procedures depicted in Scheme III.

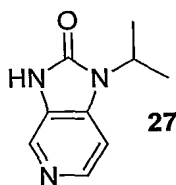


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3,4-Diaminopyridine (30 g, 274.9 mmol), ethyl acetoacetate (53.66 g, 412 mmol) and DBU (1 mL) were stirred at reflux in xylene (300 mL) under a Dean-Stark trap. After stirring for 3.5 hours, the solvent was evaporated and the residue was purified by flash chromatography (EtOAc; EtOAc:MeOH = 10:1) to give a solid which was recrystallized from CH₂Cl₂/EtOAc to afford **26** (21.45 g, 45% yield) as white crystals.

¹H NMR (CDCl₃) δ 2.19 (s, 3 H), 5.22 (s, 1 H), 5.46 (s, 1 H), 7.19 (d, J = 5.4 Hz, 1 H), 8.20 (d, J = 5.4 Hz, 1 H), 8.23 (s, 1 H); MS m/e 176 (MH⁺).

20

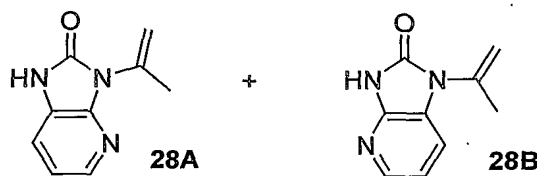


Compound **26** (1.0 g, 5.71 mmol) in the presence of 10 % palladium on carbon (0.1 g) in MeOH (10 mL) was hydrogenated in a Parr shaker at 40 psi for

25

2 days. The catalyst was removed by filtration and the filtrate was evaporated to give compound **27** as a white solid.

^1H NMR (CDCl_3) δ 1.57 (d, $J = 7.0$ Hz, 6 H), 4.72-4.76 (m, 1 H), 7.19 (d, $J = 5.8$ Hz, 1 H), 8.30 (d, $J = 5.8$ Hz, 1 H), 8.58 (s, 1 H);
MS m/e 178 (MH^+).



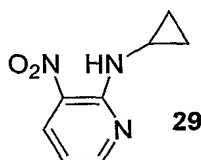
The same procedure described for compound **26** was carried out using 2,3-diaminopyridine to give **28A** and **28B** which were separated by flash chromatography (gradient, CH_2Cl_2 /acetone, 5:1 to 4:1).

Compound **28A**

^1H NMR (CD_3OD) δ 2.31 (s, 3 H), 5.40 (s, 1 H), 5.51 (s, 1 H), 7.04 (dd, $J = 5.2$, 7.7 Hz, 1 H), 7.38 (dd, $J = 1.4$, 7.7 Hz, 1 H), 8.09 (dd, $J = 1.4$, 5.2 Hz, 1 H);
MS m/e 176 (MH^+).

Compound **28B**

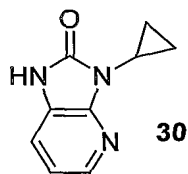
^1H NMR (CD_3OD) δ 2.26 (s, 3 H), 5.21 (s, 1 H), 5.38 (s, 1 H), 7.11 (dd, $J = 5.5$, 7.9 Hz, 1 H), 7.40 (dd, $J = 1.3$, 7.9 Hz, 1 H), 8.09 (dd, $J = 1.3$, 5.5 Hz, 1 H);
MS m/e 176 (MH^+).



2-Chloro-3-nitropyridine (7.0 g, 50.0 mmol), cyclopropylamine (3.71 g, 65 mmol) and potassium carbonate (13.82 g, 100 mmol) were stirred in CH₃CN (100 mL) at room temperature overnight and at reflux for an additional hour.

The solid was filtered and the filtrate was evaporated. Water was added to the residue and the mixture was extracted with EtOAc. The combined extracts were dried over MgSO₄ and filtered. Evaporation of the solvent gave **29** (8.40 g, 94% yield) as a dark brown solid.

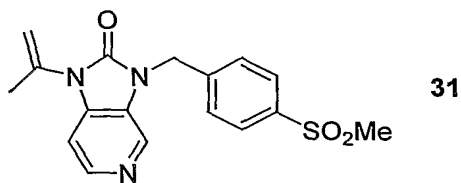
¹H NMR (CD₃OD) δ 0.63-0.69 (m, 2 H), 0.93-0.97 (m, 2 H), 3.01-3.06 (m, 1 H), 6.70-6.72 (dd, J = 4.5, 8.3 Hz, 1 H), 8.24 (bs, 1 H), 8.42 (dd, J = 1.7, 8.3 Hz, 1 H), 8.52 (dd, J = 1.7, 4.5 Hz, 1 H); MS m/e 180 (MH⁺).



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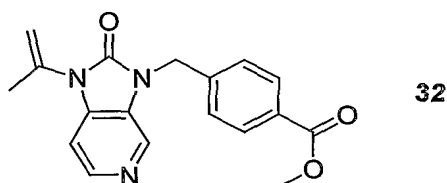
Compound **29** (8.29 g, 46.28 mmol) was reduced with iron using the procedure described for compound **7**. To the crude diamine in THF (50 mL) was added 1 equivalent of carbonyldiimidazole and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was diluted with CH₂Cl₂, washed with water, dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc / hexane, 1:1 to EtOAc / MeOH, 10: 1) to give **30** (1.93 g, 24 % yield over two steps) as a light orange solid.

¹H NMR (CDCl₃) δ 1.19 (d, J = 3.4 Hz, 2 H), 1.20 (s, 2H), 3.01-3.04 (m, 2 H), 7.02 (dd, J = 5.3, 7.7 Hz, 1 H), 7.32 (dd, J = 1.4, 7.7 Hz, 1 H), 8.12 (dd, J = 1.4 Hz, 5.3 Hz, 1 H), 9.61 (bs, 1 H); MS m/e 176 (MH⁺).



A mixture of **26** (2.0 g, 11.4 mmol), Cs₂CO₃ (5.58 g, 17.1 mmol) and *p*-methylsulfonylbenzyl chloride (2.34 g, 11.4 mmol) in acetone (50 mL) was stirred at reflux for 2 hours. The solid was removed by filtration and the filtrate was evaporated. The residue was purified by flash chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) to afford **31** (3.24 g, 83% yield) as a white solid.

¹HNMR (DMSO-d₆) δ 2.18 (s, 3 H), 3.20 (s, 3 H), 5.23 (s, 2 H), 5.26 (s, 1 H), 5.45 (d, J = 1.2 Hz, 1 H), 7.21 (d, J = 5.3 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 2 H), 7.92 (d, J = 8.4 Hz, 2 H), 8.25 (d, J = 5.1 Hz, 1H), 8.41 (s, 1 H); MS m/e 344 (MH⁺).

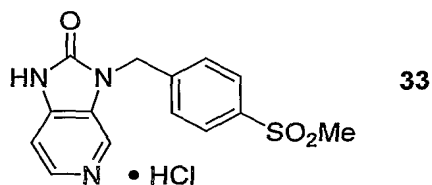


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Compound **32** was prepared using the same procedure for compound **31**, except that methylsulfonylbenzyl chloride was replaced with methyl *p*-bromomethylbenzoate.

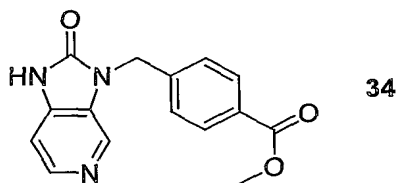
¹HNMR (DMSO-d₆) δ 2.05 (s, 3H), 3.70 (s, 3H), 5.06 (s, 2H), 5.12 (s, 1H), 5.32 (d, J=1.4 Hz, 1H), 7.07-7.09 (dd, J= 0.45, 5.4 Hz, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.80-7.82 (m, 2H), 8.11 (d, J=5.3 Hz, 1H), 8.23 (s, 1H); MS m/e 324 (MH⁺).

63



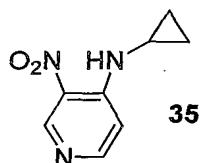
A solution of **31** (3.24 g, 9.45 mmol) in concentrated HCl (5 ml) and MeOH (50 ml) was stirred at reflux for 2 hours. The solvent was evaporated and the residue was triturated in hot MeOH to yield **33** (2.80 g, 87% yield) as a white solid as the HCl salt.

¹H NMR (DMSO-d₆) δ 3.18 (s, 3 H), 5.17 (s, 2 H), 7.07 (d, J = 5.2 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.91 (d, J = 8.2 Hz, 2 H), 8.17 (d, J = 5.0 Hz, 1 H), 8.29 (s, 1 H);
MS m/e 304 (MH⁺).



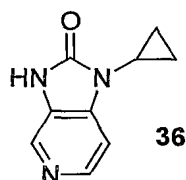
A solution of **32** (1.30 g, 4.02 mmol) in concentrated HCl (10 ml) and MeOH (10 ml) was stirred at reflux for 1 hour. The solution was neutralized with K₂CO₃ to pH 6, and extracted with EtOAc. The organic layer was dried and evaporated to dryness. The crude product was triturated with hot CH₂Cl₂ to yield **34** (0.85 g, 75% yield) as off-white solid.

¹H NMR (DMSO-d₆) δ 3.90 (s, 3 H), 5.20 (s, 2 H), 7.13 (d, J = 5.2 Hz, 1 H), 7.53 (d, J = 8.2 Hz, 2 H), 8.00 (d, J = 8.2 Hz, 2 H), 8.22 (d, J = 5.2 Hz, 1 H), 8.31 (s, 1 H);
MS m/e 284 (MH⁺).



A solution of 4-methoxy-3-nitro-pyridine (7.71 g, 50 mmol) and
5 cyclopropylamine (7.14g, 125 mmol) in EtOH (20 mL) was stirred at reflux
under a dry-ice trap condenser for 2 hours. The solvent was evaporated to give
35 as a yellow solid.

^1H NMR (CD_3OD) δ 0.72-0.75 (m, 2 H), 0.99-1.03 (m, 2 H), 2.63-2.68 (m, 1 H),
10 7.19 (d, $J = 6.2$ Hz, 1 H), 8.26 (bs, 1 H), 8.35 (d, $J = 6.2$ Hz, 1 H), 9.22 (s, 1 H);
IR (KBr, cm^{-1}) 3369, 1613, 1560, 1515, 1406, 1254, 1195, 1039, 881, 846, 769, 545;
MS m/e 180 (MH^+).



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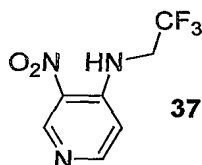
To a solution of **35** (12.28 g, 68.6 mmol) in anhydrous MeOH (120 mL)
was added 10% palladium on carbon (3 g) in several portions under nitrogen.
The reduction was carried out using a balloon containing hydrogen (1 atm) for 16
hours. The catalyst was removed by filtration through a pad of Celite and rinsed
20 with MeOH. The filtrate was concentrated to a slurry and Et_2O was added to
precipitate the diamine product as a light yellow solid (10.1g, 99% yield).

To a slurry of the diamine and polyvinylpyridine (22.0 g) in acetonitrile
(70 mL) of a 20% phosgene solution in toluene was added dropwise (70 mL,
25 135.4 mmol). After stirring at room temperature for 2 hours, the reaction was
quenched with water. Polyvinylpyridine was removed by filtration and rinsed

with MeOH. The filtrate was concentrated and Et₂O was added to precipitate product **36** (15.5g, 98% yield) as a light brown solid.

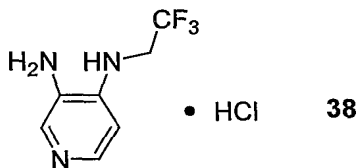
¹H NMR (CD₃OD) δ 0.95-0.98 (m, 2 H), 1.07-1.14 (m, 2 H), 2.91-2.96 (m, 1 H),
5 7.32 (dd, J = 0.5, 5.3 Hz, 1 H), 7.18 (s, 1 H), 8.21 (d, J = 5.3 Hz, 1 H);
MS m/e 176 (MH⁺).

2-Oxo-imidazopyridine **39** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced
10 with 2 equivalents of trifluoroethylamine hydrochloride and diisopropylethylamine, and the reaction was carried out in a sealed tube at 120-130 °C for 2 days.



15 ¹H NMR (CDCl₃) δ 4.02 (q, J = 7.9 Hz, 2 H), 6.83 (d, J = 5.5 Hz, 1 H), 8.43 (d over bs, 2 H), 9.28 (s, 1 H);
IR (KBr, cm⁻¹): 3287, 3241, 1629, 1611, 1363, 1254, 1150, 1047, 870;
MS m/e 222 (MH⁺);

20 Anal. Calcd for C₇H₆F₃N₃O₂ : C, 38.02; H, 2.73; N, 19.00
Found: C, 38.00; H, 2.69; N, 19.19.

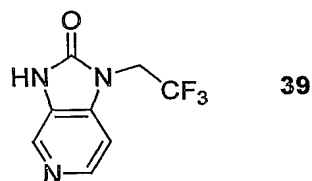


25 ¹H NMR (CD₃OD) δ 4.23 (q, J = 9.0 Hz, 2 H), 7.05 (d, J = 6.6 Hz, 1 H), 7.74 (d, J = 1.1 Hz, 1 H), 7.84 (d, J = 1.1, 6.6 Hz, 1 H);
IR (KBr, cm⁻¹): 3343, 3202, 3062, 1625, 1578, 1529, 1257, 1154, 949;

MS m/e 192 (MH^+);

Anal. Calcd for $\text{C}_7\text{H}_8\text{F}_3\text{N}_3 \cdot \text{HCl}$: C, 36.94; H, 3.99; N, 18.46

Found: C, 37.19; H, 3.86; N, 18.79.



5

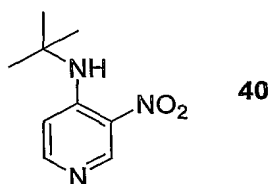
^1H NMR ($\text{DMSO}-d_6$) δ 4.99 (q, $J = 9.2$ Hz, 2 H), 7.90 (d, $J = 6.3$ Hz, 1 H), 8.61 (d, $J = 6.3$ Hz, 1 H), 8.63 (s, 1 H);

IR (KBr, cm^{-1}): 3423, 2994, 1744, 1517, 1347, 1254, 1263, 1173, 1000, 811;

10 MS m/e 218 (MH^+).

2-Oxo-imidazopyridine **41** was prepared using the same procedure described for compound **36**, except that cyclopropylamine was replaced with *t*-butylamine and the reaction was carried out in a sealed tube at 80 °C. This compound was used as a crude intermediate for the coupling reaction.

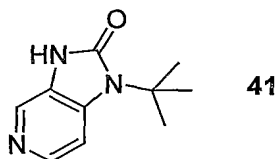
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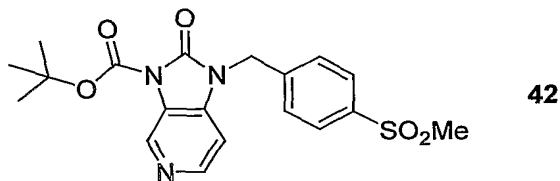


^1H NMR (CDCl_3) δ 1.54 (s, 9 H), 7.21 (d, $J = 6.3$ Hz, 1 H), 8.17 (d, $J = 6.3$ Hz, 1 H), 9.08 (s, 1 H);

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MS m/e 196 (MH^+).

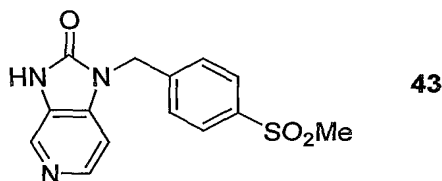




A mixture of 1,2-dihydro-2-oxo-3*H*-imidazol[4,5-*c*]pyridine-3-carboxylic acid, 1,1-dimethyl ethyl ester (470 mg, 2.0 mmol) (prepared according to the
5 procedure described by N. Meanwell et al. in *J. Org. Chem.* **1995**, *60*, 1565),
Cs₂CO₃ (978 mg, 3.0 mmol) and *p*-methylsulfonylbenzyl chloride (451 mg, 2.2
mmol) in acetone (10 mL) was stirred at reflux for 2 hours. The mixture was
filtered and the filtrate was evaporated. The residue was purified by flash
chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20 :1) to afford **42** (500 mg,
10 62% yield) as a white solid.

¹H NMR (CDCl₃) δ 1.71 (s, 9 H), 3.04 (s, 3 H), 5.15 (s, 2 H), 6.90 (m, 1 H), 7.54
(m, 2 H), 7.93 (m, 2 H), 8.40 (m, 1 H), 9.01 (m, 1 H);
MS *m/e* 404 (MH⁺).

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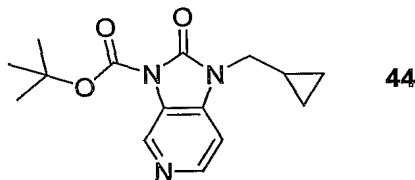


A mixture of **42** (260 mg, 0.64 mmol) and 1 N NaOH (3.22 ml) in THF (5
ml) and water (1 ml) was stirred at the ambient temperature overnight. The
20 mixture was diluted with saturated NH₄Cl and extracted with CH₂Cl₂. The
combined extracts were dried over MgSO₄ and evaporated. The residue was
trituated with EtOAc to produce **43** (180 mg, 93% yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ 3.34 (s, 3 H), 5.16 (s, 2 H), 7.19 (d, *J* = 5.2 Hz, 1 H), 7.56 (d,
J = 8.4 Hz, 2 H), 7.89 (d, *J* = 8.4 Hz, 2 H), 8.15 (d, *J* = 5.2 Hz, 1 H), 8.22 (s, 1 H),
25 11.34 (s, 1 H);
MS *m/e* 304 (MH⁺).

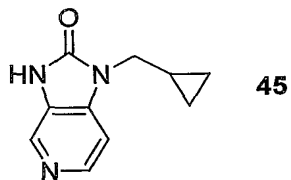
2-Oxo-imidazopyridine **45** was prepared using the same procedure for compound **43**, except that *p*-methylsulfonylbenzyl chloride was replaced with cyclopropylmethyl bromide. This compound was used as a crude intermediate for the coupling reaction.

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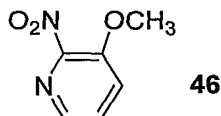
^1H NMR (CD_3OD) δ 0.44-0.45 (m, 2 H), 0.56-0.58 (m, 2 H), 1.21-1.25 (m, 1 H), 1.69 (s, 9 H), 3.79 (d, $J = 7.1$ Hz, 2 H), 7.35 (d, $J = 5.4$ Hz, 1 H), 8.34 (d, $J = 5.4$ Hz, 1 H), 8.84 (s, 1 H);
MS m/e 290 (MH^+).

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^1H NMR (CD_3OD) δ 7.54 (d, $J = 1.2$ Hz, 1 H), 8.19 (d, $J = 1.2$ Hz, 1 H), 8.23 (s, 1 H), 8.67 (s, 1 H);
MS m/e 137 (MH^+).

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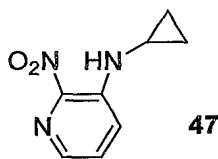
To a solution of 3-hydroxy-2-nitropyridine (100 g, 0.71 mol) in acetone (800 mL) was added potassium carbonate (148 g, 1.07 mol) followed by dimethyl sulfate (99 g, 0.79 mol). The reaction mixture was stirred vigorously using a mechanical stirrer and heated to 60 °C for 4.5 hours. The mixture was
25 filtered while still warm. The filtrate was stripped of solvent to give a crude

brown solid. The solid was diluted with water and extracted with EtOAc. The organic extracts were dried over anhydrous MgSO_4 , filtered and evaporated. The residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 1:1) to give **46** as a bright yellow solid (81 g, 74 % yield).

5

^1H NMR (CDCl_3) δ 3.98 (s, 3 H), 7.51-7.57 (m, 2 H), 8.10 (dd, $J = 1.5, 7.5$ Hz, 1 H);

MS m/e 155 (MH^+).



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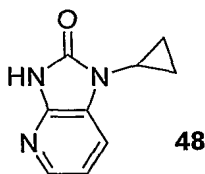
Compound **47** was obtained from **46** using the same procedure for the preparation of **35** except that the reaction was carried out with 1.5 equivalents of cyclopropylamine in a sealed tube at 120 °C for 2 days.

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^1H NMR (CDCl_3) δ 0.67-0.72 (m, 2 H), 0.89-1.00 (m, 2 H), 2.58-2.65 (m, 1 H), 7.50 (dd, $J = 4.0, 8.6$ Hz, 1 H), 7.82 ($J = 8.6$ Hz, 1 H), 7.83 (d, $J = 8.6$ Hz, 1 H), 7.97 (dd, $J = 1.4, 4.0$ Hz, 1 H);

MS m/e 155 (MH^+).

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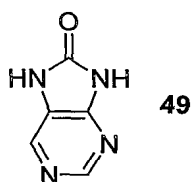


A solution of **47** (300 mg, 1.67 mmol) in MeOH (25 mL) was agitated under H_2 (10 psi) in the presence of 10% palladium on carbon (60 mg) for 15 min. The catalyst was removed by filtration through a pad of Celite. To the filtrate was added urea (402 mg, 6.70 mmol), and the mixture was evaporated. The solid residue was then heated at 170 °C for 16 hours. The resulting black

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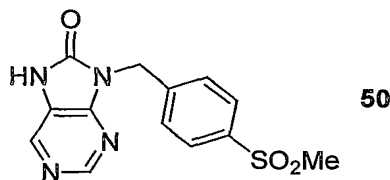
solid was heated in boiling ethanol and filtered. The filtrate was evaporated and the residue was purified by flash chromatography (gradient, straight CH₂Cl₂ to CH₂Cl₂/MeOH, 20:1) to give compound **48** as a yellow solid (82 mg, 28% yield).

- 5 ¹H NMR (CDCl₃) δ 0.99-1.04 (m, 2 H), 1.12-1.15 (m, 2 H), 2.89-2.93 (m, 1 H), 7.05 (dd, J = 5.3, 7.8 Hz, 1 H), 7.41 (dd, J = 1.3; 7.8 Hz, 1 H), 8.05 (d, J = 5.3 Hz, 1 H);
MS m/e 176 (MH⁺).



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Compound **49** was prepared from 4,5-diaminopyrimidine and urea using the same procedure described for compound **48**.

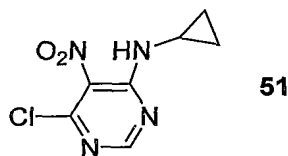


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- To a slurry of **49** (136 mg, 1.0 mmol) in THF (5 mL) was added BTPP (946 mg, 3.0 mmol) and *p*-methylsulfonylbenzyl chloride (205 mg, 1.0 mmol) at ambient temperature. After stirring overnight, the solution was diluted with
20 EtOAc, washed with water, dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) to afford compound **50** (52 mg, 34% yield) as a white solid.

- 25 ¹H NMR (CD₃OD) δ 3.08 (s, 3 H), 5.26 (s, 2 H), 7.67 (d, J = 8.4 Hz, 2 H), 7.91-7.93 (m, 2 H), 8.34 (s, 1 H), 8.74 (s, 1 H);
MS m/e 305 (MH⁺).

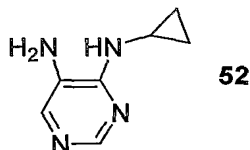
71



To a suspension of 4,6-dichloro-5-nitropyrimidine (3.88 g, 20.0 mmol) and triethylamine (4.05 g, 40.0 mmol) in THF (50 ml) was added
5 cyclopropylamine (1.14 g, 20.0 mmol) dropwise at 0 °C. After stirring at 0 °C for 2 hours, the slurry was filtered. The filtrate was diluted with EtOAc, washed with water, dried over MgSO₄, and evaporated. The residue was purified by flash chromatography (gradient, CH₂Cl₂/MeOH, 100:1 to 40:1) to afford compound **51** (2.75 g, 64% yield) as a yellow solid.

10

¹H NMR (DMSO-d₆) δ 0.61-0.64 (m, 2 H), 0.74-0.78 (m, 2 H), 2.92 (bs, 1 H), 8.43 (bs, 1 H), 8.51 (s, 1 H);
MS m/e 215 (MH⁺).



15

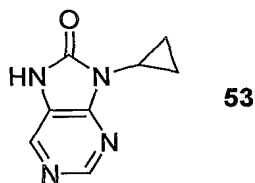
Pyrimidine **51** was reduced using catalytic hydrogenation with 10 % palladium on carbon in MeOH at 40 psi (Parr shaker) for 1 hour to afford compound **52**.

20

¹H NMR (DMSO-d₆) δ 0.74-0.76 (m, 2 H), 0.79-0.83 (m, 2 H), 3.06-3.11 (m, 1 H), 6.17 (bs, 2 H), 7.47 (d, J = 1.5 Hz, 1 H), 8.37 (d, J = 1.0 Hz, 1 H), 9.09 (d, J = 3.8 Hz, 1 H);
MS m/e 151 (MH⁺).

25

72



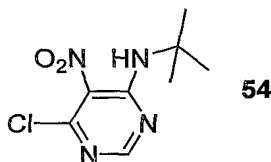
Compound **53** was obtained by cyclization of diamine **52** according to the same procedure described for compound **36** using phosgene and polyvinylpyridine.

^1H NMR (CD_3OD) δ 1.14-1.19 (m, 2 H), 1.20-1.27 (m, 2 H), 3.11-3.18 (m, 1 H), 8.47 (d, $J = 0.45$ Hz, 1 H), 9.01 (s, 1 H); MS m/e 177 (MH^+).

10

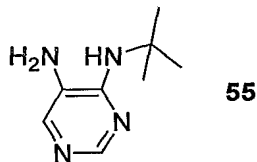
2-Oxo-imidazopyrimidine **56** was prepared using the same procedure for compound **53**, except that cyclopropylamine was replaced with *t*-butylamine. The compound was used as a crude intermediate for the coupling reaction without further purification.

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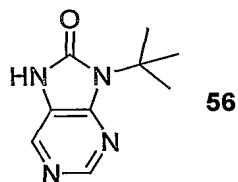
^1H NMR (CDCl_3) δ 1.52 (s, 9 H), 7.26 (bs, 1 H), 8.37 (s, 1 H); MS m/e 231 (MH^+).

20

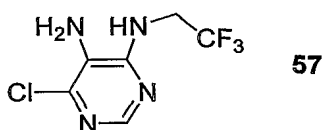


^1H NMR (CD_3OD) δ 1.57 (s, 9 H), 7.49 (d, $J = 1.3$ Hz, 1 H), 8.27 (d, $J = 1.3$ Hz, 1 H); MS m/e 167 (MH^+).

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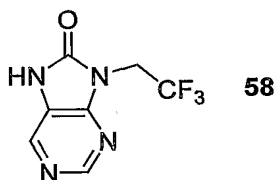


2-Oxo-imidazopyrimidine **58** was prepared according to the same
5 procedure described for compound **53**, except that cyclopropylamine was
replaced with 2,2,2-trifluoroethylamine. The crude intermediate was used in the
coupling reaction without further purification.



10

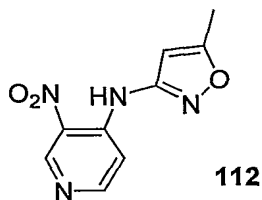
^1H NMR (CD_3OD) δ 4.30-4.36 (m, 2 H), 8.46 (s, 1 H);
MS m/e 226 (MH^+).



15

2-Oxo-imidazopyridine **113** was prepared according to the same
procedure for the preparation of **36**, except that cyclopropylamine was replaced
with 2 equivalents of 3-amino-5-methylisoxazole, and the reaction was carried
out in MeOH at 100 °C for 18 hours in a sealed pressure tube.

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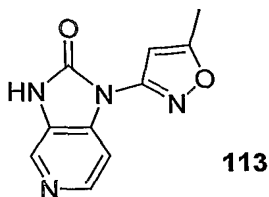


^1H NMR (CD_3OD) δ 0.88 (s, 3 H), 4.71 (s, 1 H), 6.79 (d, $J = 6.2$ Hz, 1 H), 6.95 (d, $J = 6.2$ Hz, 1 H), 7.69 (d, 1 H);

IR (KBr, cm^{-1}) 3323, 3125, 3097, 1604, 1581, 1521, 1499, 1228, 1179;

MS m/e 221 (MH^+);

- 5 Anal. Calcd for $\text{C}_9\text{H}_8\text{N}_4\text{O}_3$: C, 49.09; H, 3.66; N, 25.44
 Found: C, 49.04; H, 3.63; N, 25.06.

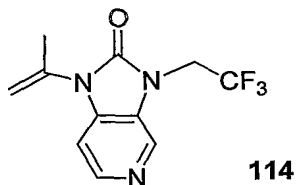


- 10 ^1H NMR (CD_3OD) δ 2.50 (s, 3 H), 6.94 (s, 1 H), 7.95 (dd, $J = 0.6, 6.55$ Hz, 1 H), 8.31 (s, 1 H), 8.32 (d, $J = 5.5$ Hz, 1 H);

IR (KBr, cm^{-1}) 3546, 3463, 2679, 1744, 1720, 1596, 1474, 1457, 1193, 1129, 809, 633;

MS m/e 217 (MH^+).

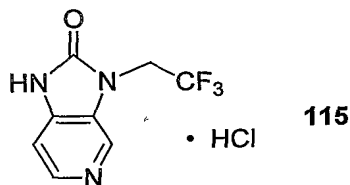
15



- A mixture of compound **26** (400 mg, 2.28 mmol) and BTPP (1.57 g, 5.02 mmol) in THF (10 mL) was stirred for 20 minutes after which 2,2,2-trifluoroethyl *p*-toluenesulfonate (605 mg, 2.40 mmol) was added to the mixture. The reaction mixture was stirred at 45 °C for 18 hours and then at 60 °C for an additional 24 hours. The solvent was evaporated and the residue was diluted with H_2O and extracted with EtOAc. The combined organic extracts were dried over MgSO_4 and evaporated. Purification by flash column chromatography (EtOAc/MeOH, 20:1) gave 295 mg (50% yield) of **114** as a white solid.
- 20
- 25

^1H NMR (CDCl_3) δ 2.24 (s, 3 H), 4.51 (q, $J = 8.6$ Hz, 2 H), 5.24 (s, 1 H), 5.43 (d, $J = 1.1$ Hz, 1 H), 7.10 (d, $J = 5.5$ Hz, 1 H), 8.39 (s, 1 H), 8.40 (d, $J = 5.5$ Hz, 1 H); IR (KBr, cm^{-1}) 3026, 1727, 1605, 1503, 1169, 1156, 1126, 827; MS m/e 258 (MH^+).

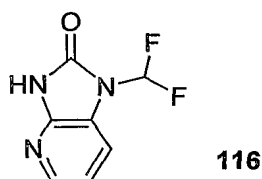
5



Compound **114** (272 mg, 1.06 mmol) and concentrated HCl (12 mL) in MeOH (20 mL) were refluxed for 72 hours. The solvent was evaporated and the residue was dried under vacuum to give 263 mg (99% yield) of compound **115** as the HCl salt.

^1H NMR ($\text{DMSO}-d_6$) δ 4.93 (q, $J = 9.2$ Hz, 2 H), 7.61 (d, $J = 6.3$ Hz, 1 H), 8.54 (d, $J = 6.3$ Hz, 1 H), 8.89 (s, 1 H); MS m/e 218 (MH^+).

15



Compound **28B** (1.2 g, 6.86 mmol) and BTPP (3.21 g, 10.28 mmol) in CH_2Cl_2 were mixed together in a sealed flask and cooled to -78°C . Chlorodifluoromethane (gas, approximately 2 g, 23.26 mmol) was bubbled into the solution in the sealed flask. The flask was sealed and the temperature was raised to 0°C for 10 minutes and then to room temperature for 3 minutes. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 . The combined extracts were dried over MgSO_4 and evaporated. To the residue was added 6 N HCl in MeOH (1:1 mixture, 10 mL). The mixture was stirred at reflux for 6 hours. The reaction was neutralized with solid Na_2CO_3 . The solvent was

20

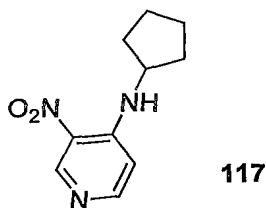
25

concentrated and the resulting aqueous solution was extracted with CH_2Cl_2 . The combined extracts were dried over MgSO_4 and evaporated. Purification by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) gave 398 mg (31% yield) of **116**.

5

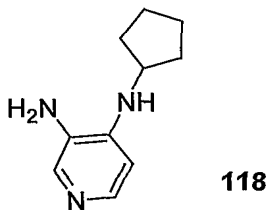
^1H NMR (CDCl_3) δ 7.14 (dd, $J = 5.7, 7.4$ Hz, 1 H), 7.36 (t, $J = 58.7$ Hz, 1 H), 7.62 (d, $J = 7.8$ Hz, 1 H), 8.21 (d, $J = 5.3$ Hz, 1 H), 9.40 (bs, 1 H); MS m/e 186 (MH^+).

10 Compound **119** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced with 2 equivalents of cyclopentylamine, and the reaction was carried out in a sealed pressure tube at 120°C for 2 hours.



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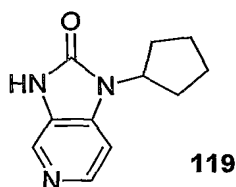
^1H NMR (CDCl_3) δ 1.62-1.69 (m, 2 H), 1.70-1.76 (m, 2 H), 1.79-1.85 (m, 2 H), 2.10-2.16 (m, 2 H), 3.96-4.01 (m, 1 H), 6.76 (d, $J = 6.2$ Hz, 1 H), 8.23 (bs, 1 H), 8.27 (d, $J = 6.2$ Hz, 1 H), 9.21 (s, 1 H);

20 MS m/e 208 (MH^+).

^1H NMR (CDCl_3) δ 1.48-1.53 (m, 2 H), 1.61-1.64 (m, 2 H), 1.69-1.74 (m, 2 H), 2.00-2.06 (m, 2 H), 3.12 (bs, 2 H), 3.77-3.83 (m, 1 H), 4.22 (bd, $J = 4.5$ Hz, 1 H), 6.47 (d, $J = 5.4$ Hz, 1 H), 7.85 (s, 1 H), 7.92 (d, $J = 5.4$ Hz, 1 H);

25

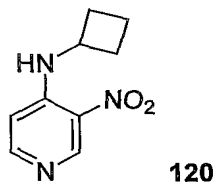
MS m/e 178 (MH^+).



- 5 ^1H NMR (DMSO-d_6) δ 1.61-1.68 (m, 2 H), 1.85-1.95 (m, 4 H), 1.97-2.02 (m, 2 H), 4.11 (bs, 1 H), 4.67-4.74 (m, 1 H), 7.20 (d, $J = 5.3$ Hz, 1 H), 8.16 (d, $J = 5.4$ Hz, 1 H), 8.19 (s, 1 H);

MS m/e 204 (MH^+).

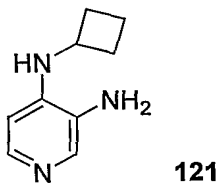
- 10 Compound **122** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced with 2 equivalents of cyclobutylamine, and the reaction was carried out in a sealed pressure tube at 100 °C.



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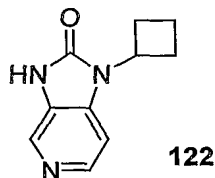
^1H NMR (CDCl_3) δ 1.89-1.97 (m, 2 H), 2.05-2.09 (m, 2 H), 2.50-2.56 (m, 2 H), 4.06-4.13 (m, 1 H), 6.56-6.62 (m, 1 H), 8.23 (s, 1 H), 8.27 (d, $J=5.6$ Hz, 1 H), 9.21 (s, 1 H);

- 20 MS m/e 194 (MH^+).

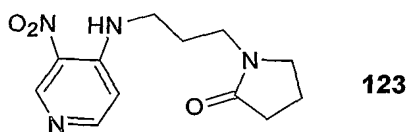


^1H NMR ($\text{DMSO}-d_6$) δ 1.70-1.79 (m, 2 H), 1.83-1.91 (m, 2 H), 2.32-2.50 (m, 2 H), 3.85-3.91 (m, 1 H), 4.59 (s, 2 H), 5.49 (d, $J=6.2$ Hz, 1H), 6.22 (d, $J=5.3$ Hz, 1 H), 7.55 (d, $J= 5.2$ Hz, 1 H), 7.63 (s, 1 H);
MS m/e 164 (MH^+).

5



^1H NMR (CD_3OD) δ 1.92-2.04 (m, 2 H), 2.43-2.49 (m, 2 H), 2.88-2.97 (m, 2 H), 4.93-4.98 (m, 1 H), 7.83 (d, $J= 6.6$ Hz, 1 H), 8.41-8.43 (m, 2 H);

10 MS m/e 190 (MH^+).

To a solution of 4-chloro-3-nitropyridine (4.9 g, 30.80 mmol) and 1-(3-aminopropyl)-2-pyrrolidinone (4.4 g, 30.80 mmol) in CH_3CN (50 mL) was added K_2CO_3 (4.25 g, 30.8 mmol) and the mixture was stirred for 8 hours. Additional 1-(3-aminopropyl)-2-pyrrolidinone (0.2 g, 1.41 mmol) was added and the mixture was stirred for 24 hours at room temperature. The mixture was filtered and concentrated to give 8.0 g (98% yield) of the compound **123** as an orange oil.

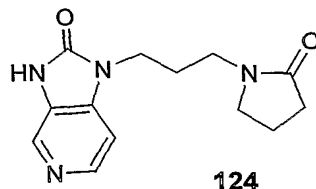
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^1H NMR (CDCl_3) δ 1.89-1.99 (m, 2 H); 2.02-2.15 (m, 2 H), 2.35 (t, $J = 8.05$ Hz, 2 H); 3.36-3.47 (m, 6 H), 6.70 (d, $J = 6.2$ Hz, 1 H), 8.28 (d, $J = 6.27$ Hz, 1 H), 8.37-8.40 (s, 1 H), 9.20 (s, 1 H);

MS m/e 264 (MH^+).

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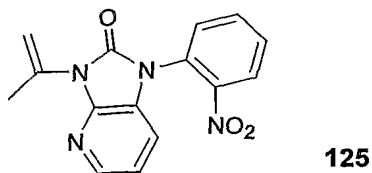
79



A mixture of **123** (2.0 g, 7.6 mmol) and 10% palladium on carbon (200 mg) in EtOH (50 mL) was hydrogenated at 50 psi for 18 hours, filtered and concentrated to give 1.6 g (90% yield) of the diamine as a black oil. The oil was dissolved in CH₂Cl₂ (40 mL), treated with carbonyl diimidazole (1.22 mg, 7.5 mmol) and stirred for 12 hours at room temperature. The solvent was evaporated and the residue was subjected to flash column chromatography (gradient, 3% MeOH/CH₂Cl₂ to 10% MeOH/CH₂Cl₂) to give 1.09 g (62% yield) of compound **124** as an orange gum.

¹H NMR (CDCl₃) δ 2.01-2.05 (m, 4 H), 2.39 (t, J = 7.9 Hz, 2 H), 3.37-3.43 (m, 4 H), 3.90 (t, J = 7.2 Hz, 2 H), 7.01 (d, J = 5.4 Hz, 1 H), 8.29 (d, J = 5.4 Hz, 1 H), 8.37 (s, 1 H);

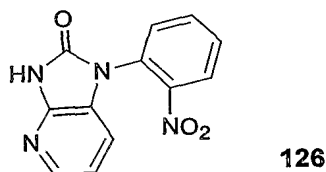
MS m/e 260 (MH⁺).



A mixture of **28A** (1.00 g, 5.71 mmol), *o*-fluoronitrobenzene (0.88 g, 6.28 mmol) and Cs₂CO₃ (5.58 g, 17.1 mmol) in DMF was stirred at room temperature for 12 hours. The reaction mixture was diluted with EtOAc and washed with water and brine, dried over MgSO₄, and concentrated. Purification by flash chromatography (gradient, CH₂Cl₂/hexane, 40:1 to 20:1) gave 1.10 g (65% yield) of **125** as a yellow foam.

¹H NMR (CDCl₃) δ 2.28-2.32 (m, 3 H), 5.45-5.49 (m, 2 H), 7.01-7.05 (m, 1 H), 7.11-7.15 (m, 1 H), 7.62-7.68 (m, 2 H), 7.80-7.84 (m, 1 H), 8.14-8.22 (m, 2 H);

MS m/e 297 (MH^+).



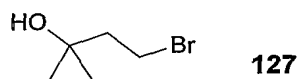
5 Compound **126** was prepared from compound **125** according to the same procedure described for compound **115**.

^1H NMR (DMSO-d_6) δ 7.06-7.09 (m, 1 H), 7.33-7.34 (m, 1 H), 7.75-7.79 (m, 1 H), 7.85-7.87 (m, 1 H), 7.94-7.98 (m, 1 H), 8.04-8.05 (m, 1 H), 8.21-8.23 (m, 1 H);

MS m/e 257 (MH^+).

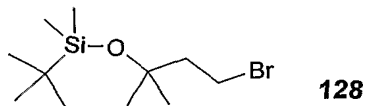
III. Preparation of R_1 -LGs:

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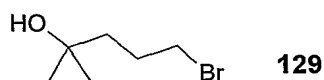
Compound **127** was prepared according to the procedure described by A. Yebga et al. in *Eur. J. Med. Chem.*, **1995**, 30, 769-777.

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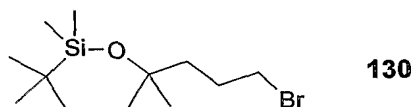
Compound **128** was prepared according to the procedure described by J. C. Heslin and C. J. Moody in *J. Chem. Soc. Perkins Trans. I*, **1988**, 6, 1417-1423.

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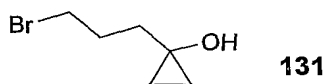
Compound **129** was prepared according to the same procedure described for compound **127**.

¹H NMR (CDCl₃) δ 1.22 (s, 6 H), 1.57-1.60 (m, 2 H), 1.92-1.98 (m, 3 H), 3.42 (t, J = 6.7 Hz, 2 H).



To neat 2,6-lutidine (11.42 g, 106.60 mmol) cooled with an ice bath to 0 °C was added *t*-butyldimethylsilyltrifluoromethane sulfonate (16.91 g, 63.96 mmol). After 30 minutes, a solution of compound **129** (7.72 g, 42.64 mmol) in CH₂Cl₂ (15 mL) was added. The resulting brown reaction mixture was stirred at 0 °C for 2.5 hours. The reaction mixture was poured onto ice (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL) and extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and evaporated. The crude brown oil was purified by flash column chromatography (pentane:Et₂O, 15:1) to give compound **130** as a colorless oil.

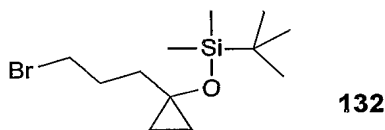
¹H NMR (CDCl₃) δ 0.07 (s, 6 H), 0.85 (s, 9 H), 1.21 (s, 6 H), 1.52-1.55 (m, 2 H), 1.93-1.99 (m, 2 H), 3.42 (t, J = 6.7 Hz, 2 H).



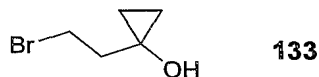
Compound **131** was prepared according to the procedure described by O. Kulinkovich et al. in *Tetrahedron Letters*, **1996**, 37, 1095-1096. To a solution of ethyl-4-bromobutyrate (16.36 g, 83.85 mmol) in Et₂O (200 mL) was added titanium (IV) isopropoxide (2.38 g, 8.39 mmol). Ethylmagnesium bromide (3.0 M in Et₂O, 58.7 mL, 176.09 mmol) was added to the mixture slowly via addition funnel over 30 minutes maintaining the temperature between 10-20 °C. The reaction mixture was stirred for 6 hours at room temperature and then poured

slowly into chilled 10% aqueous H_2SO_4 (300 mL) and stirred. The layers were separated and the aqueous layer was further extracted with Et_2O . The combined organic extracts were dried over MgSO_4 and evaporated. The crude oil was purified by flash column chromatography (gradient, hexanes/ Et_2O 3:1 to 1:1) to give 10.3g (67% yield) of compound **131** as a yellow oil.

^1H NMR (CDCl_3) δ 0.42-0.48 (m, 2 H), 0.69-0.76 (m, 2 H), 1.63-1.70 (m, 2 H), 2.05-2.14 (m, 2 H), 3.45-3.50 (m, 2 H);

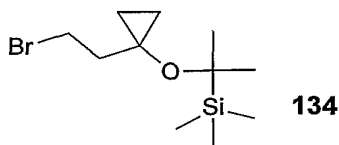


Compound **132** was prepared from compound **131** according to the same procedure described for compound **130** and was used immediately for coupling upon isolation.



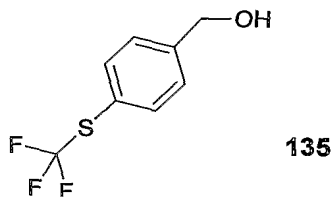
Compound **133** was prepared according to the same procedure described for compound **131** using ethyl 3-bromopropionate.

^1H NMR (CDCl_3) δ 0.51 (t, $J = 6.1$ Hz, 2 H), 0.76 (t, $J = 6.2$ Hz, 2 H), 2.07 (t, $J = 7.3$ Hz, 2 H), 3.57 (t, $J = 7.3$ Hz, 2 H).



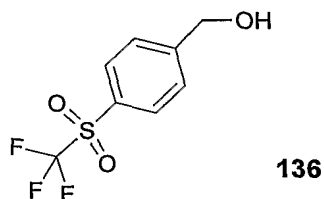
Compound **134** was prepared from compound **133** according to the same procedure described for compound **130**.

^1H NMR (CDCl_3) δ 0.10 (s, 6 H), 0.50 (t, $J = 6.3$ Hz, 2 H), 0.74 (t, $J = 6.3$ Hz, 2 H), 0.85 (s, 9 H), 2.03 (t, $J = 8.0$ Hz, 2 H), 3.56 (t, $J = 8.0$ Hz, 2 H).



A solution of 4-(trifluoromethylthio) benzoic acid (5.00 g, 22.50 mmol) and triethylamine (2.36g, 23.40 mmol) in THF (50 mL) was cooled to 0 °C and to the solution was added ethyl chloroformate (2.53 g, 23.40 mmol). The mixture was filtered and the added dropwise to a cooled solution of sodium borohydride (3.54 g, 93.38 mmol) in a mixture of H_2O and THF (1:1 ratio, 50 mL). The reaction mixture was stirred for 2 hours keeping the temperature below 15 °C and then for 18 hours at room temperature. The reaction was quenched with 1N HCl and the organic layer was separated. The aqueous layer was extracted with Et_2O and all organic layers were combined, dried over Na_2SO_4 , and evaporated. The resulting solid was dissolved in EtOAc and was washed with saturated aqueous NaHCO_3 . The organic layer was dried over Na_2SO_4 and evaporated to give 3.53 g (75% yield) of compound **135** as a white solid.

^1H NMR ($\text{DMSO}-d_6$) δ 4.57 (d, $J = 5.7$ Hz, 2 H), 5.38 (t, $J = 5.7$ Hz, 1 H), 7.48 (d, $J = 7.3$ Hz, 2 H), 7.68 (d, $J = 7.3$ Hz, 1 H).

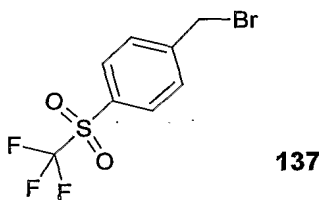


A mixture of compound **135** (3.50 g, 16.81 mmol), hydrogen peroxide (30%, 19.05 g, 168.10 mmol) and glacial acetic acid (40 mL) was stirred at 80 °C

for several minutes and then at 50 °C for 48 hours. The solution was poured into H₂O and extracted with Et₂O. The combined extracts were washed with aqueous 10% NaHCO₃, dried over Na₂SO₂, and evaporated to give 3.6 g (89% yield) of compound **136** as a white solid.

5

¹H NMR (DMSO-d₆) δ 4.70 (d, J = 7.1 Hz, 2 H), 5.61 (bs, 1 H), 7.78 (d, J = 7.2 Hz, 2 H), 8.10 (d, J = 7.2 Hz, 2 H).



10

A solution of alcohol **136** (2.0 g, 8.32 mmol) in Et₂O (50 mL) was cooled to -5 °C with an ice/salt bath. To this solution was added phosphorous tribromide and the resulting mixture was stirred at -5 °C for 5 hours and then at room temperature for 18 hours. The reaction mixture was poured into ice water and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with saturated aqueous NaHCO₃, saturated aqueous NaCl, dried over Na₂SO₄, and evaporated to give 1.45 g (56% yield) of **137** as a clear oil.

15

¹H NMR (DMSO-d₆) δ 4.87 (s, 2 H), 7.91 (d, J = 8.5 Hz, 2 H), 8.15 (d, J = 8.4 Hz, 2 H).

20

IV. Preparation of Examples of Formula I:

Unless a specific procedure is described, Examples 1-166 are prepared according to the general coupling procedures described below:

25

General Coupling Procedure of 2-Chloromethyl-benzimidazoles (II) and 2-Oxo-imidazopyridines or 2-Oxo-imidazopyrimidines in Scheme I-A.

Examples 1-3, 8-12, 14-16, 23-46, 65, 69-70, 72, 90, 94, 102, 104, 111-
5 113, 120, 122, 126, 128-131, 135-136, 140-151, 156-157, 154-155, 157 and 160-
163, and 166 were prepared according to the following procedure:

To a solution of II and 2-oxo-imidazopyridine or 2-oxo-
imidazopyrimidine (1 equivalent of each) in THF or CH₂Cl₂ or DMF is added 3-4
10 equivalents of BTPP or Cs₂CO₃. The mixture is stirred at 0 °C or room
temperature for 1-16 hours. The solvent is evaporated, and the residue is diluted
with water and extracted with EtOAc. The crude product is then purified by
chromatography on silica gel or by reverse phase preparative HPLC.

15 **General Procedure of Reacting Ia with R₂-LG in Scheme I-B.**

Examples 5-7, 18, 100, and 138 were prepared according to the following
procedure:

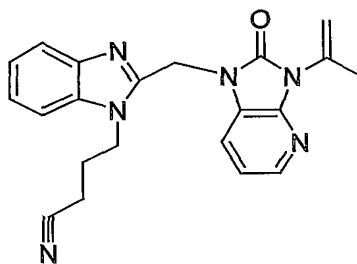
20 To a solution of Ia and 1.5-3 equivalents of BTPP, Cs₂CO₃, or BEMP on
polystyrene resin in THF or DMF is slowly added R₂-LG at room temperature.
When the reaction is completed, the solvent is evaporated or resin is filtered and
filtrate is evaporated. The residue is purified by dissolving in EtOAc or CH₂Cl₂ and
washing with water followed by flash chromatography, or by trituration of the solid
25 collected from the reaction in solvents such as MeOH, or by reverse phase
preparative HPLC.

General Procedure of Reacting V with R₁-LG in Scheme I-C.

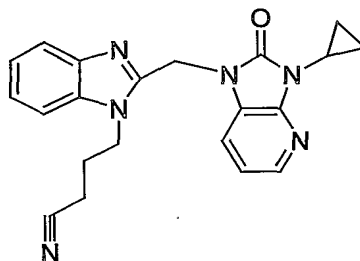
30 Examples 48, 67-68, 76, 78, 80, 82, 84, 88, 124, and 152-153 were
prepared according to the following procedure.

To a mixture of **V** and 1.5-3 equivalents of sodium hydride or BEMP on polystyrene resin in THF, DMF or CH₃CN is added R₁-LG. The reaction is stirred at temperatures ranging from 0 °C to 80 °C for 30 minutes to 18 hours. In examples where BEMP on polystyrene resin is utilized, the resin is filtered. The filtrate is evaporated and the residue is purified by flash column chromatography on silica or reverse phase preparative HPLC. In examples where sodium hydride is used as base, the reaction mixture is diluted with water, extracted with EtOAc or CH₂Cl₂, and purified by flash column chromatography on silica or reverse phase preparative HPLC.

Example 1

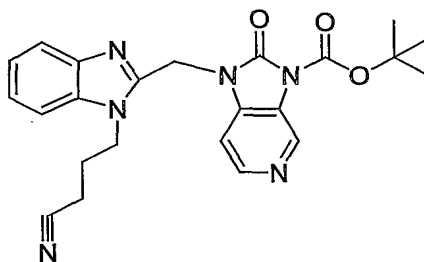


- ¹H NMR (CDCl₃) δ 2.05-2.11 (m, 2 H), 2.29 (s, 3 H), 2.50 (t, J = 7.1 Hz, 2 H), 4.58 (t, J = 7.6 Hz, 2 H), 5.36 (s, 1 H), 5.48 (s, 3 H), 7.06 (dd, J = 5.2, 7.8 Hz, 1 H), 7.35-7.45 (m, 3 H), 7.84 (d, J = 7.4 Hz, 1 H), 7.94 (bd, J = 6.4 Hz, 1 H), 8.08 (dd, J = 1.2, 5.2 Hz, 1 H);
- IR (KBr, cm⁻¹) 3423, 2952, 2243, 1698, 1656, 1618, 1452, 1403, 1336, 1247, 1152, 790, 766, 743;
- MS m/e 373 (MH⁺);
- Anal. Calcd for C₂₁H₂₀N₆O: C, 67.73; H, 5.41; N, 22.57
- Found: C, 67.35; H, 5.35; N, 22.41.

Example 2

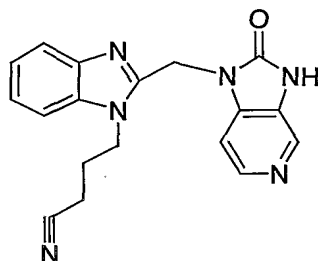
- 5 ^1H NMR (CDCl_3) δ 1.13-1.21 (m, 4 H), 2.06-2.12 (m, 2 H), 2.51 (t, $J = 7.2$ Hz, 2 H), 3.01-3.05 (m, 1 H), 4.57 (t, $J = 7.5$ Hz, 2 H), 5.42 (s, 2 H), 7.01-7.05 (m, 1 H), 7.34-7.47 (m, 3 H), 7.81-7.86 (m, 2 H), 8.10 (d, $J = 4.8$ Hz, 1 H);
IR (KBr, cm^{-1}) 3424, 2244, 1702, 1333, 1474, 1461, 1280, 1164, 789;
MS m/e 373 (MH^+).

10

Example 3

- 15 ^1H NMR (CD_3OD) δ 1.68 (s, 9 H), 2.18-2.21 (m, 2 H), 2.60 (t, $J = 7.2$ Hz, 2 H), 4.50 (t, $J = 7.6$ Hz, 2 H), 5.48 (s, 2 H), 7.23-7.25 (m, 1 H), 7.30 (t, $J = 7.2$ Hz, 1 H), 7.35 (d, $J = 5.4$ Hz, 1 H), 7.54 (d, $J = 8.0$ Hz, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 8.31 (d, $J = 5.4$ Hz, 1 H), 8.88 (s, 1 H);
MS m/e 433 (MH^+).

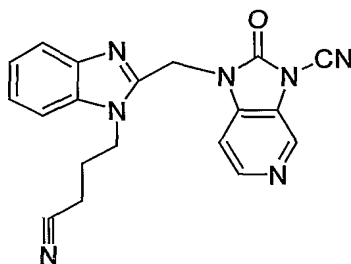
Example 4



5 The *t*-butoxycarbonyl group of Example 4 was removed by treating with aqueous 1 N NaOH solution using the procedure described for the preparation of intermediate compound 43.

¹H NMR (CD₃OD) δ 2.05-2.11 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 5.39 (s, 2 H), 7.16-7.19 (m, 1 H), 7.24-7.27 (m, 2 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.17 (d, J = 5.2 Hz, 1 H), 8.25 (s, 1 H), 11.34 (s, 1 H); MS m/e 333 (MH⁺).

15 **Example 5**



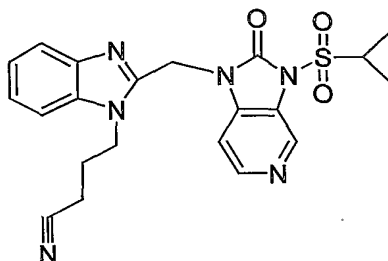
¹H NMR (DMSO-d₆) δ 2.14-2.17 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 5.52 (s, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.28 (t, J = 8.0 Hz, 1 H), 7.51 (d, J = 5.3 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.2 Hz, 1 H), 8.47 (d, J = 5.3 Hz, 1 H), 8.65 (s, 1 H);
IR (KBr, cm⁻¹) 3436, 2987, 2263, 1760, 1608, 1384, 1125, 748;
MS m/e 358 (MH⁺);

Anal. Calcd for $C_{19}H_{15}N_7O \cdot 0.6EtOAc$: C, 62.65; H, 4.87; N, 23.90

Found: C, 62.33; H, 4.76; N, 24.14.

Example 6

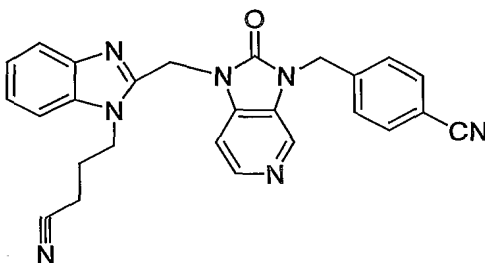
5



1H NMR (CD_3OD) δ 1.53 (d, J = 6.8 Hz, 6 H), 2.27-2.32 (m, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 4.08-4.12 (m, 1 H), 4.57 (t, J = 7.5 Hz, 2 H), 5.68 (s, 2 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 7.88 (d, J = 6.3 Hz, 2 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.94 (s, 1 H);
IR (KBr, cm^{-1}) 3420, 2314, 2251, 2075, 2008, 1752, 1623, 1509, 1369, 1180, 738;
HRMS m/e 439.1552 (MH^+).

15

Example 7



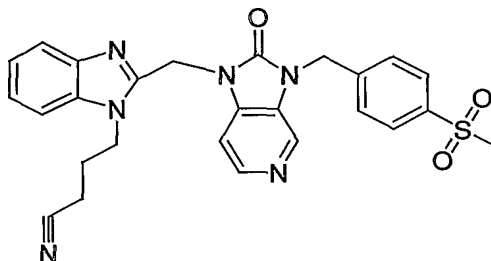
1H NMR ($DMSO-d_6$) δ 2.11-2.12 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.42 (t, J = 7.4 Hz, 2 H), 5.28 (s, 2 H), 5.50 (s, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.26 (t, J = 8.0 Hz, 1 H), 7.35 (d, J = 5.3 Hz, 1 H), 7.55-7.57 (m, 3 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.86 (d, J = 8.2 Hz), 8.24 (d, J = 5.2 Hz, 1H), 8.40 (s, 1 H);
IR (KBr, cm^{-1}) 3424, 2953, 2250, 2229, 1716, 1609, 1503, 825, 744;
MS m/e 448 (MH^+);

Anal. Calcd for $C_{26}H_{21}N_7O \cdot 0.25H_2O$: C, 69.09; H, 4.79; N, 21.69

Found: C, 69.00; H, 4.81; N, 21.77.

Example 8

5



1H NMR (DMSO- d_6) δ 2.10-2.13 (m, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 3.20 (s, 3 H), 4.43 (t, J = 7.4 Hz, 2 H), 5.30 (s, 2 H), 5.51 (s, 2 H), 7.19 (t, J = 8.0 Hz, 1 H), 7.27 (t, J = 7.2 Hz, 1 H), 7.35 (d, J = 5.2 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.62-7.65 (m, 3 H), 7.93 (d, J = 8.3 Hz, 2 H), 8.24 (d, J = 5.2 Hz, 1 H), 8.43 (s, 1 H);

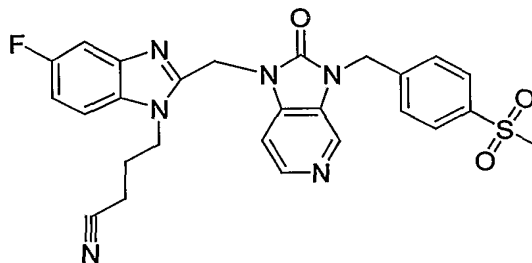
IR (KBr, cm^{-1}) 3424, 2246, 1707, 1614, 1501, 1407, 1306, 1148;

MS m/e 501 (MH^+);

Anal. Calcd for $C_{26}H_{24}N_6O_3S$: C, 62.38; H, 4.83; N, 16.78

Found: C, 62.31; H, 4.73; N, 16.75.

Example 9



20

1H NMR (DMSO- d_6) δ 2.11-2.14 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 3.21 (s, 3 H), 4.44 (t, J = 7.4 Hz, 2 H), 5.30 (s, 2 H), 5.51 (s, 2 H), 7.16 (m, 1 H), 7.36 (d, J = 5.2 Hz, 1 H), 7.40 (q, J = 2.4, 9.7 Hz, 1 H), 7.63-7.68 (m, 3 H), 7.94 (d, J = 8.4 Hz, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.44 (s, 1 H);

IR (KBr, cm^{-1}) 3423, 2926, 2248, 1707, 1613, 1602, 1148;

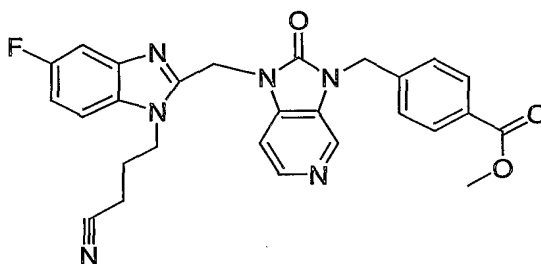
MS m/e 519 (MH^+);

Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{FN}_6\text{O}_3\text{S}$: C, 60.22; H, 4.47, N, 16.20

Found C, 60.06; H, 4.69, N, 16.21.

5

Example 10



10 ^1H NMR (DMSO-d_6) δ 2.09-2.13 (m, 2 H), 2.64 (t, $J = 7.4$ Hz, 2 H), 3.84 (s, 3 H), 4.43 (t, $J = 7.4$ Hz, 2 H), 5.26 (s, 2 H), 5.50 (s, 2 H), 7.13-7.17 (m, 1 H), 7.34-7.40 (m, 2 H), 7.51 (d, $J = 8.3$ Hz, 2 H), 7.64-7.67 (m, 1 H), 7.96-7.97 (m, 2 H), 8.23 (d, $J = 5.2$ Hz, 1 H), 8.39 (s, 1H);

IR (KBr, cm^{-1}) 3432, 2954, 2245, 1719, 1698, 1499, 1284, 1139;

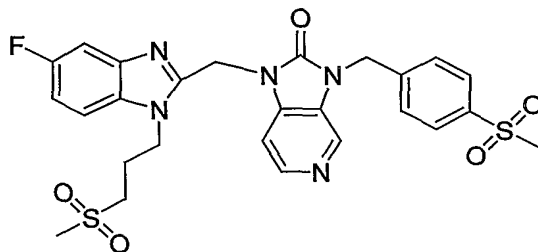
15 MS m/e 499 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{FN}_6\text{O}_3$: C, 65.05; H, 4.65; N, 16.85

Found: C, 65.25; H, 4.65; N, 16.87.

Example 11

20



^1H NMR (DMSO-d_6) δ 2.17-2.23 (m, 2 H), 3.02 (s, 3 H), 3.20 (s, 3H), 3.26 (t, $J = 8.0$ Hz, 2 H), 4.51 (t, $J = 7.7$ Hz, 2 H), 5.29 (s, 2 H), 5.50 (s, 2 H), 7.16 (dt, $J =$

2.4, 9.2 Hz, 1 H), 7.36 (d, $J = 4.9$ Hz, 1 H), 7.40 (dd, $J = 2.4, 9.5$ Hz, 1 H), 7.63 (d, $J = 8.2$ Hz, 2 H), 7.68 (dd, $J = 4.9, 8.9$ Hz, 1 H), 7.93 (d, $J = 8.3$ Hz, 2 H), 8.25 (d, $J = 5.2$ Hz, 1 H), 8.43 (s, 1 H);

IR (KBr, cm^{-1}) 3442, 2925, 2360, 1712, 1614, 1500, 1490, 1296, 1147, 761, 530;

5 MS m/e 572 (MH^+);

Anal. Calcd for $\text{C}_{26}\text{H}_{26}\text{FN}_5\text{O}_5\text{S}_2$:

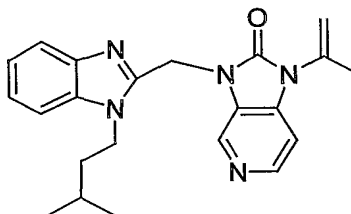
C, 54.62; H, 4.58; N, 12.25

Found:

C, 54.48; H, 4.69; N, 12.14.

Example 12

10



^1H NMR (CDCl_3) δ 0.98 (s, 3 H), 0.95 (s, 3 H), 1.44-1.52 (m, 2 H), 1.60-1.73 (m, 1 H), 2.25 (s, 3 H), 4.28-4.33 (m, 2 H), 5.20 (s, 1 H), 5.41 (s, 3 H), 7.02 (d, $J = 5.1$ hz, 1 H), 7.27-7.31 (m, 3 H), 7.77-7.80 (m, 1 H), 8.31 (d, $J = 5.1$ Hz, 1 H), 8.73 (s, 1 H);

MS m/e 376 (MH^+);

IR (KBr, cm^{-1}) 2957, 1712, 1603, 1494, 1398, 1330, 1167, 1138, 816, 740;

Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}$:

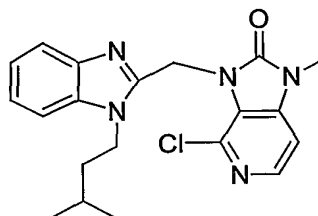
C, 70.38; H, 6.71; N, 18.65

20

Found:

C, 70.24; H, 6.67; N, 18.71.

Example 13



25

To a solution of 4-chloro-1-methyl-1,3-dihydro-imidazo[4,5 c]pyridin-2-one (Salor of Aldrich Chemical, 100 mg, 0.55 mmol) in DMF (10 mL) was added sodium hydride (26 mg, 60% dispersion in mineral oil) at room temperature.

After stirring for 30 min, a neutral form of compound 4 (155 mg, 0.654 mmol)

- 5 was added. The resulting mixture was stirred overnight and evaporated. The residue was diluted with water and extracted with Et₂O. The combined extracts were dried over MgSO₄ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc, then EtOAc/MeOH, 20:1 to 10:1) to give the Example 13 (78 mg, 38% yield).

10

¹H NMR (CDCl₃) δ 1.07 (d, J = 6.3 Hz, 6 H), 1.72-1.86 (m, 3 H), 3.52 (s, 3 H), 4.27 (t, J = 7.7 Hz, 2 H), 5.64 (s, 2 H), 6.98 (d, J = 5.3 Hz, 1 H), 7.18-7.30 (m, 2 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.66 (d, J = 7.4 Hz, 1 H), 8.13 (d, J = 5.3 Hz, 1 H); IR (KBr, cm⁻¹) 3449, 2954, 1735, 1613, 1586, 1503, 1441, 1133, 775;

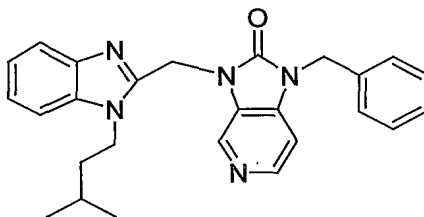
- 15 MS m/e 384 (MH⁺);

Anal. Calcd for C₂₀H₂₂ClN₅O • 1.10 H₂O: C, 59.50; H, 6.04; N, 17.35

Found: C, 59.46; H, 5.47; N, 16.68

Example 14

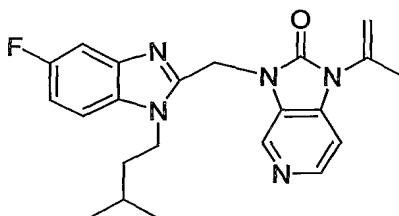
20



¹H NMR (CDCl₃) δ 1.07 (d, J = 6.1 Hz, 6 H), 1.78-1.84 (m, 3 H), 4.42 (bt, J = 8.0 Hz, 2 H), 5.21 (s, 2 H), 5.77 (s, 2 H), 7.14 (d, J = 6.2 Hz, 1 H), 7.33-7.49 (m, 8 H), 7.94 (d, J = 8.0 Hz, 1 H), 8.34 (d, J = 6.3 Hz, 1 H), 9.00 (s, 1 H);

25

MS m/e 376 (MH⁺).

Example 15

5 ^1H NMR (CD_3OD) δ 0.97 (d, $J = 6.3$ Hz, 6 H), 1.44-1.49 (m, 2 H), 1.62-1.73 (m, 1 H), 2.25 (s, 3 H), 4.27-4.33 (m, 2 H), 5.21 (s, 1 H), 5.38 (s, 2 H), 5.42 (s, 1 H), 7.02-7.08 (m, 2 H), 7.23 (dd, $J = 4.5, 9.0$ Hz, 1 H), 7.45 (dd, $J = 2.4, 9.3$ Hz, 1 H), 8.33 (d, $J = 5.1$ Hz, 1 H), 8.17 (s, 1 H);

IR (KBr, cm^{-1}) 2960, 1713, 1605, 1495, 1455, 1399, 1333, 1163, 1140, 848, 813;

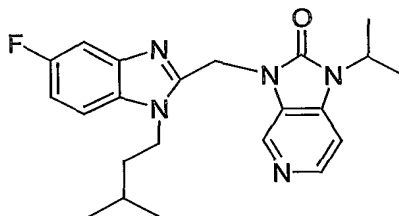
10 MS m/e 394 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{FN}_5\text{O}$: C, 67.16; H, 6.15; N, 17.80

Found: C, 67.25; H, 5.96; N, 17.88.

Example 16

15



^1H NMR (CDCl_3) δ 0.97 (d, $J = 6.9$ Hz, 6 H), 1.43-1.50 (m, 2 H), 1.55 (d, $J = 7.2$ Hz, 6 H), 1.55-1.75 (m, 1 H), 4.26-4.31 (m, 2 H), 4.70-4.80 (m, 1 H), 5.37 (s, 2 H), 7.01-7.08 (m, 2 H), 7.22 (dd, $J = 4.8, 8.9$ Hz, 1 H), 7.44 (dd, $J = 2.7, 9.3$ Hz, 1 H), 8.29 (d, $J = 5.4$ Hz, 1 H), 8.68 (s, 1 H);

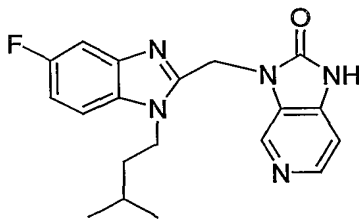
IR (KBr, cm^{-1}) 2956, 1706, 1493, 1456, 1389, 1332, 1133, 1113, 847;

MS m/e 396 (MH^+);

Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{FN}_5\text{O} \cdot 0.33\text{H}_2\text{O}$: C, 65.82; H, 6.69; N, 17.44

25

Found: C, 65.83; H, 6.30; N, 17.43.

Example 17

- 5 A solution of Example 15 (4.0 g, 10.17 mmol) in a mixture of MeOH (10 mL) and 6 N HCl (20 mL) was stirred at reflux overnight. The solution was cooled to room temperature and neutralized with concentrated NaOH solution, and evaporated. The residue was taken up with CH₂Cl₂, dried over MgSO₄, and evaporated. The residue was triturated with hot EtOAc and filtered to give
- 10 Example 17 (3.22 g, 90% yield) as a white solid.

¹H NMR (CDCl₃) δ 0.99 (d, J = 6.6 Hz, 6 H), 1.50-1.55 (m, 2 H), 1.71-1.77 (m, 1 H), 4.25-4.31 (m, 2 H), 5.36 (s, 2 H), 6.97 (d, J = 5.1 Hz, 1 H), 7.06 (dt, J = 2.4, 9.3 Hz, 1 H), 7.23 (dd, J = 4.5, 8.7 Hz, 1 H), 7.43 (dd, J = 2.4, 9.3 Hz, 1 H), 8.29

15 (d, J = 5.1 Hz, 1 H), 8.62 (s, 1 H), 9.89 (bs, 1 H);

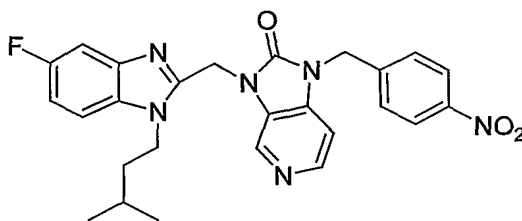
IR (KBr, cm⁻¹) 2958, 1720, 1622, 1491, 1455, 1139, 1014, 958, 894, 813;

MS m/e 375 (MH⁺);

Anal. Calcd for C₁₉H₂₀FN₅O: C, 64.58; H, 5.70; N, 19.82

Found: C, 64.26; H, 5.58; N, 19.85.

20

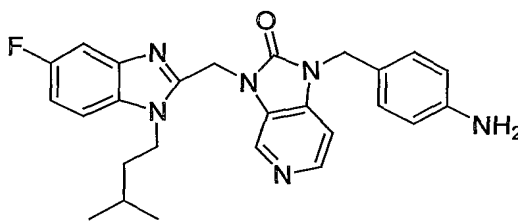
Example 18

¹H NMR (CDCl₃) δ 0.99 (d, J = 6.7 Hz, 6 H), 1.54-1.59 (m, 2 H), 1.69-1.73 (m, 1 H), 4.29 (t, J = 9.2 Hz, 2 H), 5.20 (s, 2 H), 5.43 (s, 2 H), 6.86 (d, J = 5.4 Hz, 1 H), 7.05 (dt, J = 2.4, 9.1 Hz, 1 H), 7.24 (dd, J = 4.5, 8.9 Hz, 1 H), 7.41 (dd, J = 2.4, 9.3 Hz, 1 H), 7.49 (d, J = 8.7 Hz, 2 H), 8.21 (d, J = 8.7 Hz, 2 H), 8.29 (d, J = 5.2 Hz, 1 H), 8.76 (s, 1 H);
IR (KBr, cm⁻¹) 3424, 2959, 1716, 1611, 1524, 1492, 1346, 1176, 1137, 800;
MS m/e 489 (MH⁺).

Anal. Calcd for C₂₆H₂₅FN₃O₃: C, 63.92; H, 5.16; N, 17.20

Found: C, 63.95; H, 5.13; N, 17.22.

Example 19



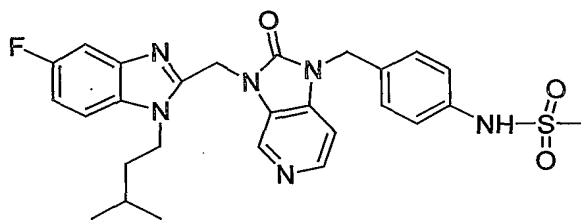
A mixture of Example 18 (1.52 g, 3.11 mmol) and 10% palladium on carbon (150 mg) in MeOH (50 mL) and concentrated hydrochloric acid (1 mL) was agitated under hydrogen at 55 psi for 1.5 hours. The reaction mixture was filtered through a pad of Celite, rinsing thoroughly with MeOH. The filtrate was evaporated and dried under vacuum to give Example 19 as an HCl salt (1.82 g, quantitative yield).

¹H NMR (CD₃OD) δ 1.09 (d, J = 6.0 Hz, 6 H), 1.84-1.90 (m, 3 H), 4.64 (t, J = 7.6 Hz, 2 H), 5.40 (s, 2 H), 5.94 (s, 2 H), 7.43-7.47 (m, 3 H), 7.52 (dd, J = 2.3, 8.1 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 6.5 Hz, 1 H), 7.93 (dd, J = 4.2, 9.1 Hz, 1 H), 8.59 (d, J = 6.4 Hz, 1 H), 9.01 (s, 1 H);
IR (KBr, cm⁻¹) 3411, 2869, 1748, 1655, 1621, 1517, 1496, 1130, 810;
MS m/e 459 (MH⁺);

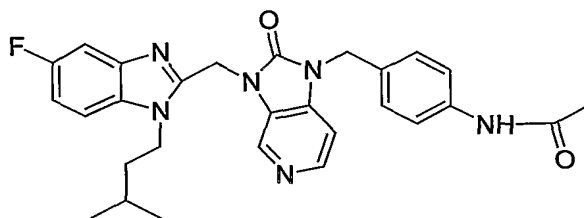
Anal. Calcd for C₂₆H₂₇FN₆O₃•3HCl•2.5H₂O: C, 50.95; H, 5.76; N, 13.71

Found: C, 50.72; H, 5.47; N, 13.66.

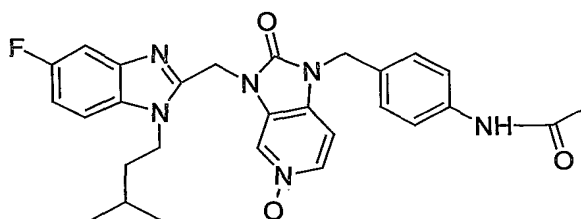
Example 20



- 5 To a mixture of Example 19 (350 mg, 0.66 mmol) and triethylamine (200 mg, 1.98 mmol) in CH₂Cl₂ cooled to 0 °C was added methanesulfonyl chloride (75 mg, 0.66 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 16 hours. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed with saturated aqueous sodium bicarbonate solution
- 10 (10 mL) and brine solution (10 mL). The aqueous layer was back-extracted with CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄, and evaporated. Trituration of the resulting pale yellow solid with Et₂O gave the title compound (quantitative yield).
- 15 ¹H NMR (CD₃OD) δ 1.06 (d, J = 6.3 Hz, 6 H), 1.75-1.81 (m, 3 H), 2.93 (s, 3 H), 4.46 (t, J = 8.2 Hz, 2 H), 5.28 (s, 2 H), 5.64 (s, 2 H), 7.18 (t, J = 2.5, 9.2 Hz, 1 H), 7.23-7.29 (m, 3 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.60 (dd, J = 4.4, 8.9 Hz, 1 H), 7.77 (d, J = 6.5 Hz, 1 H), 8.48 (d, J = 6.7 Hz, 1 H), 8.78 (s, 1 H);
- IR (KBr, cm⁻¹) 3441, 2959, 1736, 1617, 1515, 1332, 1150, 1040, 821;
- 20 MS m/e 537 (MH⁺);
- Anal. Calcd for C₂₇H₂₉FN₆O₃S•4.5H₂O: C, 52.50; H, 6.20; N, 13.61
- Found: C, 52.20; H, 5.79; N, 12.79.

Example 21

- 5 To a mixture of Example 19 (400 mg, 0.75 mmol) and triethylamine (229 mg, 2.26 mmol) in CH₂Cl₂ cooled to 0 °C was added acetyl chloride (74 mg, 0.94 mmol) followed by a catalytic amount of dimethylaminopyridine (10 mg). The reaction was allowed to warm to room temperature and a pale yellow precipitate came out of solution. After 1 hour, the reaction mixture was diluted with CH₂Cl₂
- 10 and washed with saturated aqueous sodium bicarbonate solution and brine. The aqueous layer was back-extracted with CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄, and evaporated. Trituration of the resulting white solid with Et₂O gave Example 21 (321 mg, 85% yield).
- 15 ¹H NMR (CD₃OD) δ 0.96 (d, J = 0.96 Hz, 6 H), 1.54-1.59 (m, 2 H), 1.67-1.70 (m, 1 H), 2.10 (s, 3 H), 4.36 (t, J = 8.2 Hz, 2 H), 5.13 (s, 2 H), 5.51 (s, 2 H), 7.11 (dt, J = 2.5, 9.2 Hz, 1 H), 7.21 (d, J = 5.4 Hz, 1 H), 7.30 (dd, J = 2.4, 9.3 Hz, 1 H), 7.37 (d, J = 8.6 Hz, 2 H), 7.49 (dd, J = 4.5, 9.0 Hz, 1 H), 7.54 (d, J = 8.6 Hz, 2 H), 8.19 (d, J = 5.4 Hz, 1 H), 8.35 (s, 1 H);
- 20 IR (KBr, cm⁻¹) 3424, 2960, 1724, 1691, 1610, 1517, 1507, 1455, 1402, 1319, 1136, 810;
- MS m/e 501 (MH⁺);
- Anal. Calcd for C₂₈H₂₉FN₆O₂•0.5H₂O: C, 66.00; H, 5.93; N, 16.49
- Found: C, 65.79; H, 6.12; N, 16.29.

Example 22

5 To a solution of the Example 20 (50 mg, 0.10 mmol) in DMF (5 mL) was added *m*-chloroperbenzoic acid (34 mg, 0.20 mmol). The mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure. The resulting residue was triturated with water and filtered. The aqueous filtrate was extracted with EtOAc and the combined extracts were dried
10 over MgSO₄, and evaporated. The residue combined with the solid obtained from trituration were subjected to flash chromatography (gradient, CH₂Cl₂/5% ammonium hydroxide in MeOH, 40:1 to 20:1) to give Example 22 as a white solid (21 mg, 41% yield).

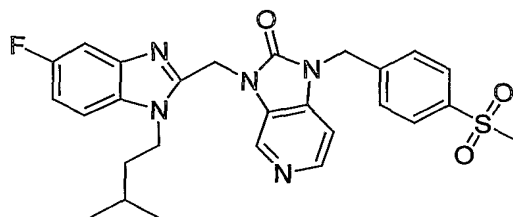
15 ¹H NMR (DMSO-d₆) δ 0.95 (d, J = 6.5 Hz, 6 H), 1.57-1.60 (m, 2 H), 1.66-1.74 (m, 1 H), 2.02 (s, 3 H), 4.32 (t, J = 7.7 Hz, 2 H), 5.05 (s, 2 H), 5.41 (s, 2 H), 7.13 (t, J = 8.7 Hz, 1 H), 7.24 (d, J = 6.7 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 1 H), 7.41 (d, J = 8.6 Hz, 1 H), 7.54 (d, J = 8.2 Hz, 1 H), 7.55-7.59 (m, 1 H), 7.96 (d, J = 6.3 Hz, 1 H), 8.37 (s, 1 H);

20 IR (KBr, cm⁻¹) 3428, 2956, 1720, 1678, 1600, 1551, 1514, 1465, 1407, 1320, 1162, 1146, 802;

MS m/e 517 (MH⁺);

Anal. Calcd for C₂₈H₂₉FN₆O₃•0.5H₂O: C, 63.99; H, 5.75; N, 15.99

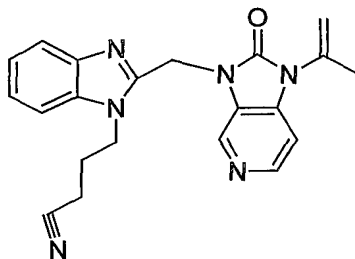
Found: C, 64.08; H, 5.57; N, 15.82.

Example 23

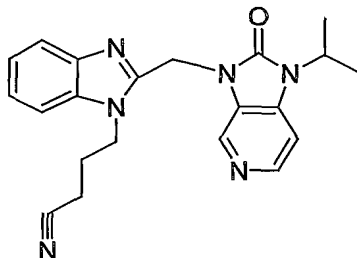
- 5 ^1H NMR (CD_3OD) δ 0.98 (d, J = 6.6 Hz, 6 H), 1.59-1.64 (m, 2 H), 1.69-1.73 (m, 1 H), 3.09 (s, 3 H), 4.39 (t, J = 8.1 Hz, 2 H), 5.31 (s, 2 H), 5.52 (s, 2 H), 7.12 (dt, J = 2.5, 9.2 Hz, 1 H), 7.23 (d, J = 5.4 Hz, 1 H), 7.29 (dd, J = 2.4, 9.2 Hz, 1 H), 7.51 (dd, J = 4.5, 8.9 Hz, 1 H), 7.66 (d, J = 8.4 Hz, 2 H), 7.94 (d, J = 8.4 Hz, 2 H), 8.22 (d, J = 1.7 Hz, 1 H), 8.39 (s, 1 H);
- 10 IR (KBr, cm^{-1}) 3423, 2959, 1715, 1613, 1602, 1497, 1454, 1407, 1307, 1148, 1090, 808, 520;
- MS m/e 522 (MH^+).

Example 24

15



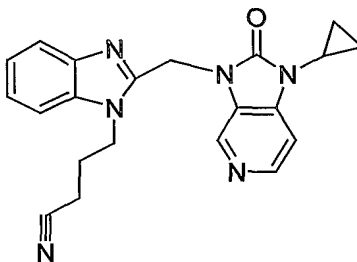
- ^1H NMR (CD_3OD) δ 1.85-1.90 (m, 2 H), 1.90 (s, 3 H), 2.27 (t, J = 7.5 Hz, 2 H), 4.29-4.34 (t, J = 7.5 Hz, 2 H), 5.03 (s, 1 H), 5.65 (s, 1 H), 6.86 (d, J = 5.5 Hz, 1 H), 7.12-7.22 (m, 3 H), 7.60-7.63 (m, 1 H), 8.16 (d, J = 5.5 Hz, 1 H), 8.65 (s, 1 H);
- 20 IR (KBr, cm^{-1}) 3396, 2244, 1710, 1660, 1604, 1493, 1458, 1399, 1332, 1166, 1140, 824, 742;
- MS m/e 373 (MH^+);
- Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O} \cdot 0.25 \text{H}_2\text{O}$: C, 66.92; H, 5.48; N, 22.30
- 25 Found: C, 66.58; H, 5.56; N, 22.34.

Example 25

5

^1H NMR (CDCl_3) δ 1.56 (d, $J = 6.9$ Hz, 6 H), 1.98-2.08 (m, 2 H), 2.45 (t, $J = 7.2$ Hz, 2 H), 4.49 (t, $J = 7.2$ Hz, 2 H), 4.70-4.74 (m, 1 H), 5.40 (s, 2 H), 7.06 (d, $J = 5.2$ Hz, 1 H), 7.33-7.39 (m, 3 H), 7.78-7.81 (m, 1 H), 8.31 (d, $J = 5.2$ Hz, 1 H), 8.81 (s, 1 H);

10 IR (KBr, cm^{-1}) 3412, 2981, 2246, 1700, 1608, 1496, 1459, 1391, 1117, 748;
MS m/e 375 (MH^+).

Example 26

15

^1H NMR (CDCl_3) δ 1.03-1.06 (m, 2 H), 1.97-1.24 (m, 2 H), 2.13-2.18 (m, 2 H), 2.47 (t, $J = 4.2$ Hz, 2 H), 2.96-3.00 (m, 1 H), 4.51 (t, $J = 4.4$ Hz, 2 H), 4.16 (s, 2 H), 7.27-7.35 (m, 4 H), 7.38 (dd, $J = 0.8, 4.2$ Hz, 1 H), 7.77 (dd, $J = 0.9, 4.4$ Hz, 1 H), 8.37 (d, $J = 3.4$ Hz, 1 H), 8.56 (s, 1 H);

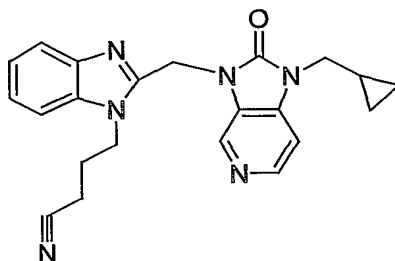
20

IR (KBr, cm^{-1}) 3405, 2245, 1702, 1608, 1500, 1408, 1172, 1024, 820, 743;
MS m/e 373 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_8\text{O} \cdot 0.875\text{H}_2\text{O}$: C, 64.98; H, 5.64; N, 21.65

Found: C, 65.06; H, 5.36; N, 21.51.

Example 27



5

¹H NMR (CD₃OD) δ 0.53-0.54 (m, 2 H), 0.64-0.66 (m, 2 H), 1.31-1.37 (m, 1 H), 2.30-2.34 (m, 2 H), 2.68 (t, J = 7.2 Hz, 2 H), 4.02 (d, J = 7.2 Hz, 2 H), 4.63 (t, J = 7.4 Hz, 2 H), 5.72 (s, 2 H), 7.39 (t, J = 7.0 Hz, 1 H), 7.43 (t, J = 7.1 Hz, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 7.73 (d, J = 8.1 Hz, 2 H), 7.92 (d, J = 6.5 Hz, 1 H), 8.55 (d, J = 6.5 Hz, 1 H), 8.81 (s, 1 H);

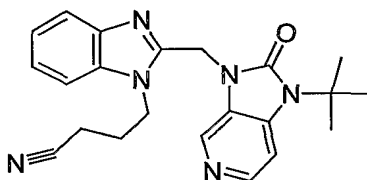
10

IR (KBr, cm^{-1}) 3448, 2250, 1748, 1676, 1522, 1201, 1131, 720;

MS m/e 387 (MH⁺).

Example 28

15

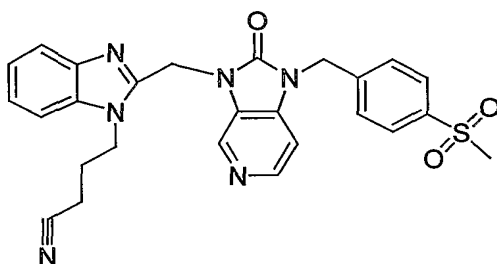


¹H NMR (CDCl₃) δ 1.81 (s, 9 H), 2.05-2.06 (m, 2 H), 2.46 (t, J = 7.2 Hz, 2 H), 4.48 (t, J = 7.6 Hz, 2 H), 5.38 (s, 2 H), 7.31-7.36 (m, 4 H), 7.78 (m, 1 H), 8.24 (d, J = 5.8 Hz, 1 H), 8.84 (s, 1 H);

20

IR (KBr, cm^{-1}) 3406, 2937, 2246, 1706, 1493, 1458, 1387, 1157, 1138, 746;

MS m/e 389 (MH⁺).

Example 29

5 ^1H NMR ($\text{DMSO}-d_6$) δ 2.09-2.12(m, 2 H), 2.63 (t, $J = 7.4$ Hz, 2 H), 4.43 (t, $J = 7.5$ Hz, 2 H), 5.28 (s, 2 H), 5.52 (s, 2 H), 7.21 (t, $J = 7.2$ Hz, 1 H), 7.26 (t, $J = 7.2$ Hz, 1 H), 7.57 (d, $J = 8.0$ Hz, 1 H), 7.60-7.63 (m, 4 H), 7.92 (d, $J = 8.4$ Hz, 2 H), 8.23 (d, $J = 5.3$ Hz, 1 H), 8.50 (s, 1 H);

IR (KBr, cm^{-1}) 3426, 2246, 1716, 1407, 1150, 760;

10 MS m/e 501 (MH^+);

Anal. Calcd for $\text{C}_{27}\text{H}_{28}\text{FN}_5\text{O}_3\text{S}$:

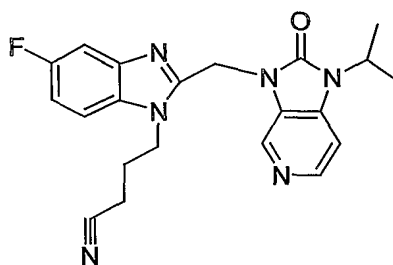
C, 62.17; H, 5.17; N, 13.43

Found:

C, 62.03; H, 5.45; N, 13.34.

Example 30

15



20 ^1H NMR (CDCl_3) δ 1.54 (d, $J = 7.0$ Hz, 6 H), 1.99-2.05 (m, 2 H), 2.45 (t, $J = 7.2$ Hz, 2 H), 4.47 (t, $J = 7.6$ Hz, 2 H), 4.70 (m, 1H), 5.36 (s, 2 H), 7.06-7.10 (m, 2 H), 7.27-7.30 (m, 1 H), 7.45 (q, $J = 2.4, 9.1$ Hz, 1 H), 8.31 (d, $J = 4.0$ Hz, 1 H), 8.78 (s, 1 H);

IR (KBr, cm^{-1}) 3432, 2953, 2360, 2245, 1718, 1698, 1284, 1139;

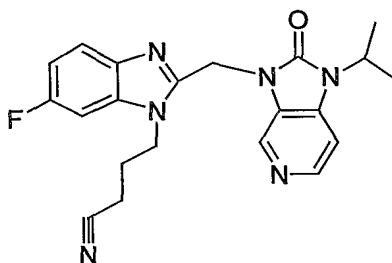
MS m/e 393 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{FN}_6\text{O}$:

C, 64.27; H, 5.39; N, 21.41

Found: C, 64.23, H, 5.44; N, 21.24.

Example 31



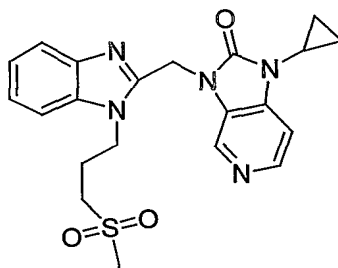
5

^1H NMR (CDCl_3) δ 1.53 (d, $J = 7.0$ Hz, 6 H), 1.96-2.03 (m, 2 H), 2.45 (t, $J = 7.2$ Hz, 2 H), 4.41 (t, $J = 7.6$ Hz, 2 H), 4.70 (m, 1 H), 5.34 (s, 2 H), 6.99-7.06 (m, 3 H), 7.67-7.70 (m, 1 H), 8.29 (d, $J = 4.0$ Hz, 1H), 8.76 (s, 1 H);

10 IR (KBr, cm^{-1}) 3423, 2941, 2247, 1710, 1492, 1390, 808;

MS m/e 393 (MH^+).

Example 32



15

^1H NMR (CDCl_3) δ 1.03-1.06 (m, 2 H), 1.17-1.22 (m, 2H), 2.25-2.31 (m, 2 H), 2.93 (s, 3 H), 2.98-3.01 (m, 1 H), 3.10 (t, $J = 7.4$ Hz, 2 H), 4.54 (t, $J = 7.5$ Hz, 2 H), 5.42 (s, 2 H), 7.25-7.39 (m, 4 H), 7.76 (d, $J = 7.1$ Hz, 1 H), 8.36 (d, $J = 5.3$ Hz, 1 H), 8.79 (s, 1 H);

20

IR (KBr, cm^{-1}) 3423, 2927, 1718, 1608, 1499, 1459, 1409, 1311, 1289, 1128, 748;

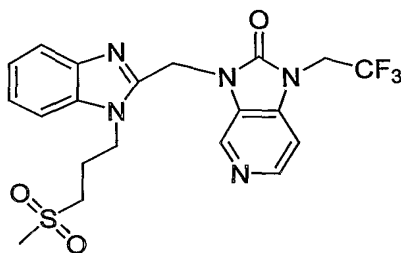
MS m/e 426(MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_3\text{S}$:

C, 59.27; H, 5.44; N, 16.45

Found:

C, 59.03; H, 5.52; N, 16.31.

Example 33

5 ^1H NMR (DMSO- d_6) δ 2.13-2.20 (m, 2 H), 3.01 (s, 3 H), 3.26 (t, $J = 7.8$ Hz, 2 H), 4.50 (t, $J = 7.5$ Hz, 2 H), 4.91 (q, $J = 9.3$ Hz, 2 H), 5.53 (s, 2 H), 7.20 (t, $J = 7.3$ Hz, 1 H), 7.28 (t, $J = 7.7$ Hz, 1 H), 7.45 (d, $J = 5.3$ Hz, 1 H), 7.64 (d, $J = 8.1$ Hz, 1 H) 8.32 (d, $J = 5.3$ Hz, 1 H), 8.52 (s, 1 H);

IR (KBr, cm^{-1}) 3441, 1725, 1498, 1460, 1408, 1294, 1265, 1167, 1125, 746;

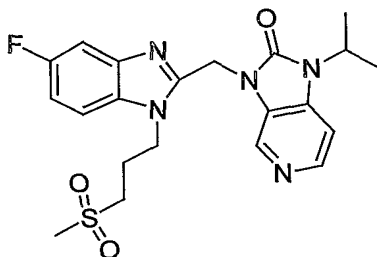
10 MS m/e 468 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_5\text{O}_3\text{S} \cdot 0.375 \text{H}_2\text{O}$: C, 50.66; H, 4.41; N, 14.76

Found: C, 50.83; H, 4.34; N, 14.41.

Example 34

15



20 ^1H NMR (CD_3OD) δ 1.47 (d, $J = 6.9$ Hz, 6 H), 2.14-2.17 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.8$ Hz, 2 H), 4.50 (d, $J = 7.5$ Hz, 2 H), 4.63-4.66 (m, 1 H), 5.44 (s, 2 H), 7.16 (dt, $J = 2.5, 9.2$ Hz, 1 H), 7.41-7.45 (m, 2 H), 7.67 (dd, $J = 4.8, 8.9$ Hz, 1 H), 8.23 (d, $J = 5.4$ Hz, 1 H), 8.47 (s, 1 H);

IR (KBr, cm^{-1}) 3423, 2984, 2937, 1702, 1608, 1495, 1457, 1391, 1293, 1135, 1116, 963, 809;

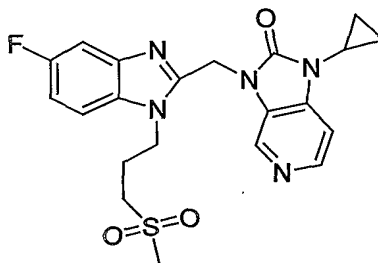
MS m/e 446 (MH^+);

Anal. Calcd for $C_{21}H_{24}FN_5O_3S$:

C, 56.61; H, 5.43; N, 15.71

Found:

C, 56.46; H, 5.55; N, 15.62.

Example 35

5

1H NMR (CD_3OD) δ 0.91-0.93 (m, 2 H), 1.06-1.07 (m, 2 H), 2.99-3.01 (m, 1 H), 3.00 (s, 3 H), 3.23 (t, $J = 7.7$ Hz, 2 H), 4.49 (t, $J = 7.5$ Hz, 2 H), 5.41 (s, $J = 2$ H), 7.15 (dt, $J =$, 1 H), 7.29 (dd, $J = 2.0, 5.3$ Hz, 1 H), 7.43 (dd, $J = 2.5, 9.8$ Hz, 1 H), 7.67 (dd, $J = 4.7, 8.9$ Hz, 1 H), 8.26 (d, $J = 5.3$ Hz, 1 H), 8.44 (s, 1 H);

10 IR (KBr, cm^{-1}) 3423, 3014, 1708, 1609, 1498, 1455, 1415, 1315, 1294, 1171, 1131, 957, 819;

MS m/e 444 (MH^+);Anal. Calcd for $C_{21}H_{22}FN_5O_3S$:

C, 56.87; H, 5.00; N, 15.79

Found:

C, 56.76; H, 5.15; N, 15.69.

15

Example 35 was converted to an oxalate salt by adding 1 equivalent of oxalic acid to a MeOH solution of 35 and evaporating the solvent.

1H NMR (CD_3OD) δ 2.26 (s, 3 H), 2.26-2.36 (m, 2 H), 2.64 (t, $J = 7.5$ Hz, 2 H), 4.62 (t, $J = 7.5$ Hz, 2 H), 5.29 (s, 1 H), 5.45 (s, 1 H), 5.58 (s, 2 H), 7.16 (dd, $J = 5.4, 8.1$ Hz, 1 H), 7.34-7.44 (m, 2 H), 7.54-7.71 (m, 2 H), 7.70 (d, $J = 8.1$ Hz, 1 H), 8.01 (dd, $J = 0.9, 5.4$ Hz, 1 H);

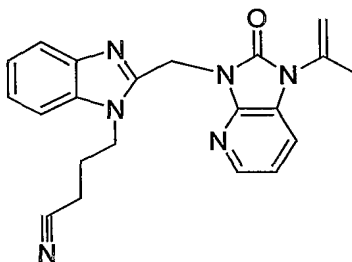
20 IR (KBr, cm^{-1}) 3405, 2954, 2244, 1702, 1611, 1476, 1456, 1400, 1276, 1188, 1158, 795, 749;

25 MS m/e 373 (MH^+);Anal. Calcd for $C_{21}H_{20}N_6O \cdot C_2H_2O_4 \cdot 0.25H_2O$:

C, 59.16; H, 4.86; N, 18.00

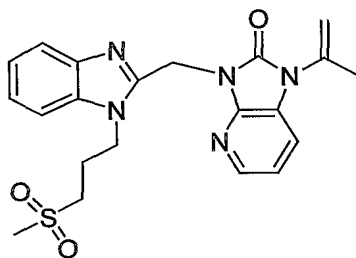
Found:

C, 58.90; H, 4.83; N, 18.24.

Example 36

- 5 ^1H NMR (CDCl_3) δ 2.19-2.45 (m, 2 H), 2.45 (s, 3 H), 2.48 (t, $J = 7.1$ Hz, 2 H), 4.61 (t, $J = 7.4$ Hz, 2 H), 5.19 (s, 1 H), 5.34 (s, 1 H), 5.48 (s, 2 H), 7.03 (dd, $J = 5.2, 7.9$ Hz, 1 H), 7.26-7.33 (m, 3 H), 7.80 (d, $J = 8.0$ Hz, 1 H), 8.10 (dd, $J = 1.4, 5.2$ Hz, 1 H).

10

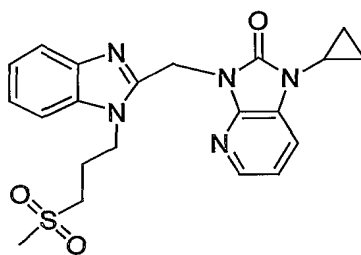
Example 37

- 15 ^1H NMR (CDCl_3) δ 2.28-2.34 (s over m, 5 H), 2.94 (s, 3 H), 3.16 (t, $J = 7.2$ Hz, 2 H), 4.59 (t, $J = 7.9$ Hz, 2 H), 5.37 (s, 1 H), 5.47 (s, 1 H), 5.54 (s, 2 H), 7.08 (dd, $J = 5.3, 7.8$ Hz, 1 H), 7.39-7.43 (m, 2 H), 7.51 (d, $J = 7.7$ Hz, 1 H), 7.85 (d, $J = 7.3$ Hz, 1 H), 8.05 (bs, 1 H), 8.09 (dd, $J = 1.0, 5.2$ Hz, 1 H);

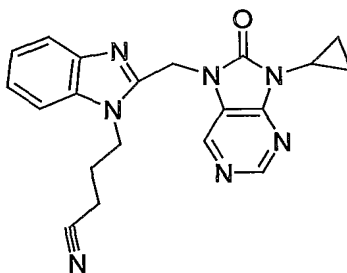
IR (KBr, cm^{-1}) 3423, 1708, 1618, 1453, 1402, 1295, 1131, 750;

MS m/e 426 (MH^+);

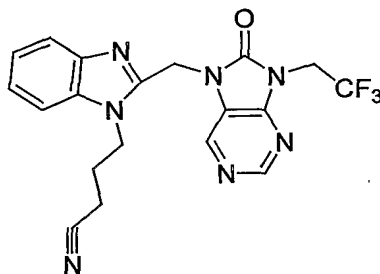
- 20 Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_3\text{S}$: C, 59.28; H, 5.44; N, 16.45
 Found: C, 59.11; H, 5.36; N, 16.35.

Example 38

- 5 ^1H NMR (CDCl_3) δ 1.06-1.11 (m, 4 H), 2.49-2.54 (m, 2 H), 2.94-2.99 (m, 1 H), 3.24 (t, $J = 6.7$ Hz, 2 H), 4.75 (t, $J = 7.1$ Hz, 2 H), 5.70 (s, 2 H), 7.05 (dd, $J = 5.3$, 7.7 Hz, 1 H), 7.37-7.44 (m, 3 H), 7.54 (d, $J = 8.0$ Hz, 1 H), 7.91 (d, $J = 8.0$ Hz, 1 H), 7.98 (d, $J = 4.8$ Hz, 1 H);
IR (KBr, cm^{-1}) 3435, 1716, 1617, 1486, 1460, 1425, 1295, 1131, 747;
10 MS m/e 426 (MH^+).

Example 39

- 15 ^1H NMR ($\text{DMSO}-d_6$) δ 1.02-1.07 (m, 4 H), 2.08-2.14 (m, 2 H), 2.64 (t, $J = 7.4$ Hz, 2 H), 3.02-3.03 (m, 1 H), 4.42 (t, $J = 7.4$ Hz, 2 H), 5.44 (s, 1 H), 7.19 (t, $J = 7.5$ Hz, 1 H), 7.28 (t, $J = 7.2$ Hz, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 7.63 (d, $J = 8.0$ Hz, 1 H), 8.46 (s, 1 H), 8.66 (s, 1 H);
20 IR (KBr, cm^{-1}) 3452, 2244, 1731, 1718, 1612, 1488, 1422, 1407, 1317, 746;
MS m/e 374 (MH^+);
Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_7\text{O}$: C, 64.33; H, 5.12; N, 26.25
Found: C, 64.00; H, 5.20; N, 26.12.

Example 40

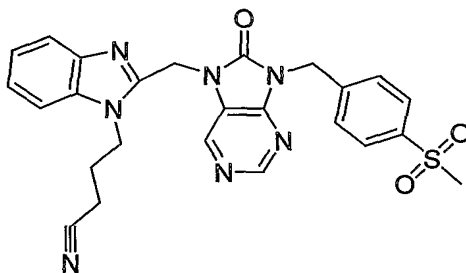
¹H NMR (CDCl₃) δ 2.07-2.13 (m, 2 H), 2.48 (t, J = 6.9 Hz, 2 H), 4.52 (d, J = 7.6 Hz, 2 H), 4.59-4.64 (m, 2 H), 5.47 (s, 2 H), 7.33-7.44 (m, 3 H), 7.80 (d, J = 7.5 Hz, 1 H), 8.76 (s, 1 H), 8.88 (s, 1 H);

MS m/e 416 (MH⁺);

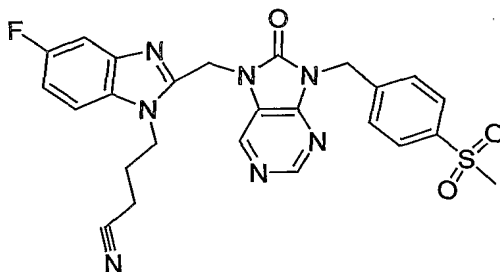
Anal. Calcd for C₁₉H₁₆F₃N₇O: C, 54.94; H, 3.88; N, 23.60

Found: C, 54.87; H, 3.78; N, 23.66.

10

Example 41

¹H NMR (CDCl₃) δ 2.12-2.15 (m, 2 H), 2.43 (t, J = 7.0 Hz, 2 H), 3.02 (s, 3 H), 4.51 (t, J = 7.4 Hz, 2 H), 5.22 (s, 2 H), 5.45 (s, 2 H), 7.32-7.42 (m, 3 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.77-7.79 (m, 1 H), 7.91-7.93 (m, 2 H), 8.73 (s, 1 H), 8.83 (s, 1 H); MS m/e 502 (MH⁺).

Example 42

5 ^1H NMR (CDCl_3) δ 2.12-2.15 (m, 2 H), 2.44 (t, $J = 7.0$ Hz, 2 H), 3.02 (s, 3 H), 4.49 (t, $J = 7.4$ Hz, 2 H), 5.23 (s, 2 H), 5.41 (s, 2 H), 7.10-7.14 (m, 1 H), 7.32-7.34 (m, 1 H), 7.43 (dd, $J = 2.4, 9.0$ Hz, 1 H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.92 (d, $J = 8.3$ Hz, 2 H), 8.74 (s, 1 H), 8.80 (s, 1 H);

IR (KBr, cm^{-1}) 3441, 2928, 2244, 1718, 1609, 1492, 1406, 1300, 1150;

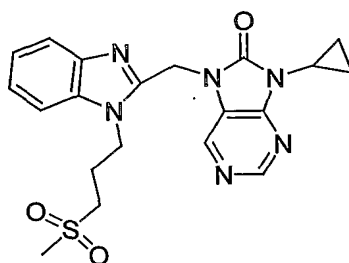
10 MS m/e 520 (MH^+);

Anal. Calcd. for $\text{C}_{25}\text{H}_{22}\text{FN}_3\text{O}_3\text{S}$: C, 57.79; H, 4.26; N, 18.87

Found: C, 57.49; H, 4.11; N, 18.55.

Example 43

15



20 ^1H NMR (CDCl_3) δ 1.17-1.18 (m, 2 H), 2.31-2.37 (m, 2 H), 2.97 (s, 3 H), 3.01-3.06 (m, 1 H), 3.15 (t, $J = 7.2$ Hz, 2 H), 4.58 (t, $J = 7.5$ Hz, 2 H), 5.41 (s, 1 H), 7.30-7.36 (m, 2 H), 7.42 (d, $J = 7.4$ Hz, 1 H), 7.76-7.78 (dd, $J = 1.2, 7.2$ Hz, 1 H), 8.73(s, 1 H), 8.74 (s, 1 H);

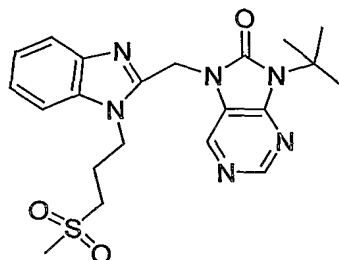
IR (KBr, cm^{-1}) 3424, 1721, 1615, 1493, 1407, 1313, 1126, 750;

MS m/e 427 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_6\text{OS} \cdot \text{H}_2\text{O}$: C, 54.04; H, 5.44; N, 18.91

Found: C, 53.95; H, 5.54; N, 18.75.

Example 44



5

^1H NMR (CDCl_3) δ 1.84 (s, 9 H), 2.30-2.35 (m, 2 H), 3.13 (t, $J = 7.2$ Hz, 2H), 4.58 (t, $J = 7.6$ Hz, 2 H), 5.38 (s, 1 H), 7.30-7.35 (m, 2 H), 7.42 (d, $J = 7.4$ Hz, 1 H), 7.76-7.78 (dd, $J = 1.2, 7.2$ Hz, 1 H), 8.66 (s, 1 H), 8.73 (s, 1 H);

10 IR (KBr, cm^{-1}): 3431, 2927, 1718, 1616, 1469, 1444, 1469, 1444, 1296, 1134, 747;

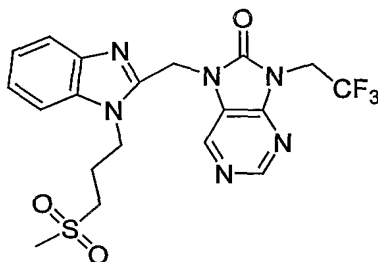
MS m/e 443 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_3\text{S} \cdot \text{H}_2\text{O}$: C, 55.86; H, 6.03; N, 18.61

Found: C, 55.87; H, 5.88; N, 18.44.

15

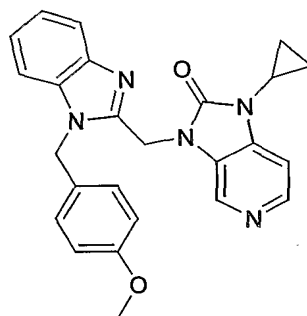
Example 45



^1H NMR (CDCl_3) δ 2.25-2.29 (m, 2 H), 2.97 (s, 3 H), 3.14 (t, $J = 7.0$ Hz, 2 H), 4.56-4.64 (m, 4 H), 5.49 (s, 2 H), 7.32-7.39 (m, 2 H), 7.44 (d, $J = 7.4$ Hz, 1 H), 7.78-7.80 (dd, $J = 1.4, 7.2$ Hz, 1 H), 8.76 (s, 1 H), 8.85 (s, 1 H);

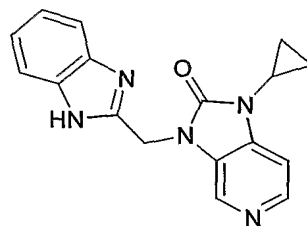
20

MS m/e 469 (MH^+).

Example 46

- 5 ^1H NMR (CDCl_3) δ 0.71-0.74 (m, 2 H), 1.03-1.07 (m, 2 H), 2.63-2.66 (m, 1 H), 3.66 (s, 3 H), 5.39 (s, 2 H), 5.47 (s, 2 H), 6.50 (m, 4 H), 6.99 (d, $J = 5.3$ Hz, 1 H), 7.20 (d, $J = 8.0$ Hz, 1 H), 7.26 (m, 1 H), 7.31 (m, 1 H), 7.85 (d, $J = 8.0$ Hz, 1 H), 8.27 (d, $J = 5.0$ Hz, 1 H), 8.53 (s, 1 H);
MS m/e 426 (MH^+).

10

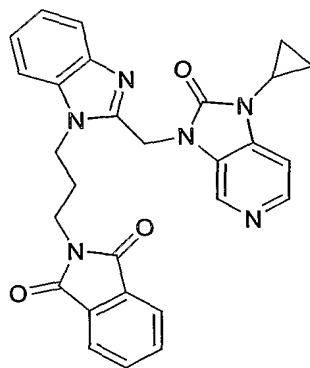
Example 47

- 15 A stirred suspension of Example 46 (11.75 g, 27.6 mmol) in CH_3CN (150 mL) was treated with ceric ammonium nitrate (CAN, 60.60 g, 110 mmol) and diluted with water (25 mL) to give a homogeneous solution which was stirred at room temperature for 24 hours. The mixture was concentrated *in vacuo* to a volume of 50 mL, then diluted with H_2O (100 mL) and again concentrated until
20 100 mL remained and a yellow solid had precipitated from solution. The yellow solid was isolated from the chilled suspension by filtration and was identified as the 4-methoxybenzaldehyde by-product. The filtrate was then diluted with H_2O to 400 mL and MeOH (600 mL) was added. To the resulting solution was added a

saturated aqueous solution of sodium potassium tartrate until the pH of the solution reached 6 and a very finely divided powder precipitated. The reaction mixture was centrifuged and the liquid was decanted away from the solid and concentrated *in vacuo*. The residue was redissolved in water (250 mL) and the
5 resulting solution was extracted with CH₂Cl₂ (8 x 100 mL). The organic extracts were combined and concentrated *in vacuo* to a brown glassy solid which was redissolved in minimum CH₂Cl₂. After a few minutes, a beige powder precipitated from solution. Et₂O was added to the mixture and the solid was isolated by filtration, rinsed with Et₂O, and dried under high vacuum to give 6.62
10 g (79 % yield) of Example 47 as a beige powder.

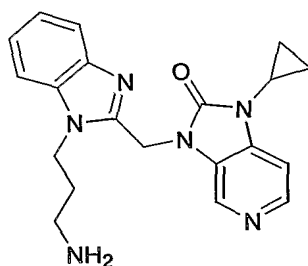
¹H NMR (DMSO-d₆) δ 0.92-0.97 (m, 2 H), 1.06-1.10 (m, 2 H), 2.97-3.01 (m, 1 H), 5.30 (s, 2 H), 7.14-7.17 (m, 2 H), 7.30 (d, J = 5.4 Hz, 1 H), 7.50 (bs, 2 H), 8.25-8.28 (m, 2 H), 12.54 (bs, 1 H);
15 MS m/e 306 (MH⁺).

Example 48



20

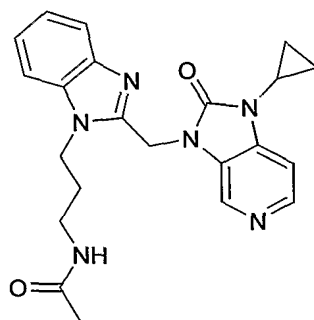
¹H NMR (CDCl₃) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.09-2.15 (m, 2 H), 2.99-3.03 (m, 1 H), 3.82 (t, J = 6.8 Hz, 2 H), 4.42 (t, J = 7.9 Hz, 2 H), 5.36 (s, 2 H), 7.21-7.28 (m, 3 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.69-7.74 (m, 3 H), 7.81-7.85 (m, 2 H), 8.35 (d, J = 5.0 Hz, 1 H), 8.79 (s, 1 H);
25 MS m/e 493 (MH⁺).

Example 49

5 Example **48** (2.58 g, 5.24 mmol) was treated with hydrazine hydrate (2.62 g, 52.4 mmol) in MeOH (100 mL) and the mixture was heated to reflux for 5 hours. The resulting mixture was passed through a 50 mL bed of AG 50W-X2 strong cation exchange resin (Bio-Rad Laboratories), and the bed was rinsed with MeOH (300 mL). The yellow eluent was discarded, and the product was eluted
10 from the resin with 2M ammonia in MeOH (500 mL). The ammonia eluent was concentrated *in vacuo* to give 1.85 g (97 % yield) of Example **49** as an off-white powder.

¹H NMR (DMSO-d₆) δ 0.92 (s, 2 H), 1.07 (d, J = 5.8, 2 H), 1.74 (t, J = 6.8 Hz, 2 H), 2.57 (t, J = 6.2 Hz, 2 H), 2.99-3.01 (m, 1 H), 4.39 (t, J = 7.1 Hz, 2 H), 5.43 (s, 2 H), 7.17 (t, J = 7.4 Hz, 1 H), 7.24 (t, J = 7.5 Hz, 1 H), 7.29 (d, J = 5.1 Hz, 1 H), 7.58 (t, J = 8.6 Hz, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.39 (s, 1 H);
15 MS m/e 363 (MH⁺).

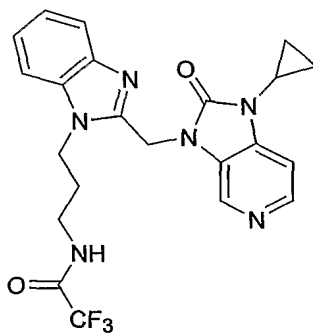
20

Example 50

A mixture of Example 49 (0.050 g, 0.14 mmol) and polystyrene diisopropylethylamine resin (PS-DIEA resin, Argonaut, 0.075 g, 0.28 mmol) in anhydrous CH_2Cl_2 (1 mL) was treated with acetic anhydride (0.141 g, 1.38 mmol) and stirred at room temperature for 18 hours. Solids which precipitated from solution were redissolved by the addition of chloroform (1 mL), and the reaction mixture was filtered to remove the resin. The filtrate was concentrated *in vacuo*, and the residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.074 g (>100% yield) of the trifluoroacetic acid salt of Example 50 as a glassy, colorless solid.

^1H NMR (DMSO-d_6) δ 0.99-1.02 (m, 2 H), 1.13-1.17 (m, 2 H), 1.84 (s, 3 H), 1.95 (t, $J = 7.3$ Hz, 2 H), 3.14-3.17 (m, 3 H), 4.41 (t, $J = 7.5$ Hz, 2 H), 5.57 (s, 2 H), 7.25 (t, $J = 7.4$ Hz, 1 H), 7.33 (t, $J = 7.4$ Hz, 1 H), 7.58 (d, $J = 8.0$ Hz, 1 H), 7.68 (d, $J = 8.1$ Hz, 1 H), 7.83 (d, $J = 6.4$ Hz, 1 H), 7.99 (t, $J = 5.2$ Hz, 1 H), 8.62 (d, $J = 6.2$ Hz, 1 H), 8.83 (s, 1 H);
MS m/e 405 (MH^+).

Example 51

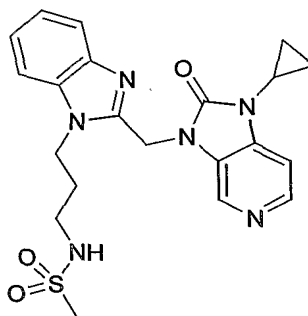


Example 51 was prepared according to the same procedure described for Example 50 using trifluoroacetic anhydride.

^1H NMR (DMSO-d_6) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.03-2.08 (m, 2 H), 3.14-3.18 (m, 1 H), 3.33-3.37 (m, 2 H), 4.42 (t, $J = 7.5$ Hz, 2 H), 5.54 (s, 2 H), 7.20-7.23 (m, 1 H), 7.29-7.23 (m, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 7.65 (d, $J = 8.1$

Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.81 (s, 1 H), 9.54-9.56 (m, 1 H);
MS m/e 459 (MH⁺).

5

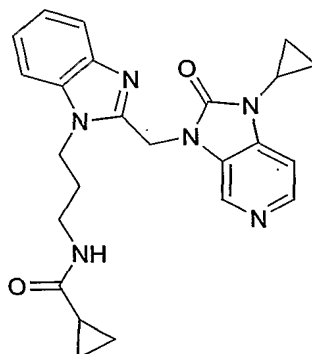
Example 52

Example 52 was prepared according to the same procedure described for
10 Example 50 using methanesulfonyl chloride.

¹H NMR (DMSO-d₆) δ 1.04-1.07 (m, 2 H), 1.14-1.17 (m, 2 H), 2.12 (t, J = 7.4 Hz, 2 H), 2.96 (s, 3 H), 3.16-3.18 (m, 3 H), 4.58 (t, J = 7.6 Hz, 2 H), 5.82 (s, 2 H), 7.23-7.25 (m, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.54 (t, J = 7.7 Hz, 1 H), 7.75 (d, J =
15 8.1 Hz, 1 H), 7.88 (d, J = 6.5 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 1 H), 8.66 (d, J = 6.5 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 441 (MH⁺).

Example 53

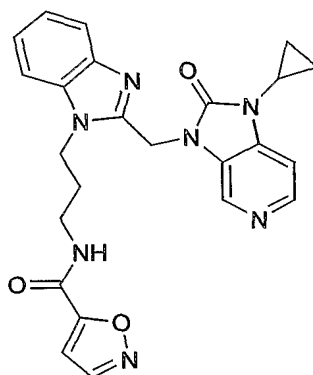
20



Example 53 was prepared according to the same procedure described for Example 50 using cyclopropanecarbonyl chloride.

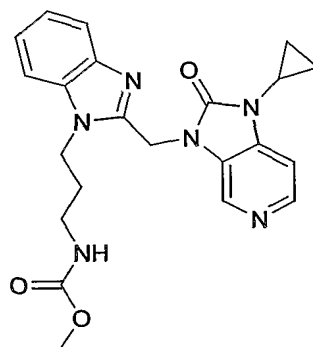
¹H NMR (DMSO-d₆) δ 0.63-0.69 (m, 4 H), 0.98-1.02 (m, 2 H), 1.13-1.17 (m, 2 H), 1.53-1.58 (m, 1 H), 1.94-2.00 (m, 2 H), 3.14-3.20 (m, 3 H), 4.40 (t, J = 7.4 Hz, 2 H), 5.55 (s, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 6.3 Hz, 1 H), 8.21 (t, J = 5.1 Hz, 1 H), 8.61 (d, J = 6.2 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 431 (MH⁺).

Example 54



Example 54 was prepared according to the same procedure described for Example 50 using isoxazole-5-carbonyl chloride.

¹H NMR (DMSO-d₆) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.06-2.12 (m, 2 H), 3.13-3.17 (m, 1 H), 3.39-3.43 (m, 2 H), 4.46 (t, J = 7.5 Hz, 2 H), 5.56 (s, 2 H), 7.06 (s, 1 H), 7.22 (t, J = 7.4 Hz, 1 H), 7.30 (t, J = 7.4 Hz, 1 H), 7.56 (d, J = 8.1 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.60 (d, J = 6.2 Hz, 1 H), 8.75 (s, 1 H), 8.81 (s, 1 H), 9.08 (t, J = 5.5 Hz, 1 H);
MS m/e 458 (MH⁺).

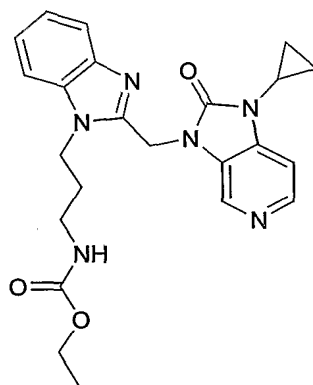
Example 55

5 Example **55** was prepared according to the same procedure described for Example **50** using methyl chloroformate.

^1H NMR (DMSO- d_6) δ 0.90-0.93 (m, 2 H), 1.03-1.09 (m, 2 H), 1.80-1.86 (m, 2 H), 2.98-3.02 (m, 1 H), 3.05-3.08 (m, 2 H), 3.53 (s, 3 H), 4.35 (t, $J = 7.5$ Hz, 2 H),
10 5.38 (s, 2 H), 7.17 (t, $J = 7.7$ Hz, 1 H), 7.23-7.29 (m, 3 H), 7.57 (d, $J = 8.2$ Hz, 2 H), 8.25 (d, $J = 5.0$ Hz, 1 H), 8.40 (s, 1 H);
MS m/e 421 (MH^+).

Example 56

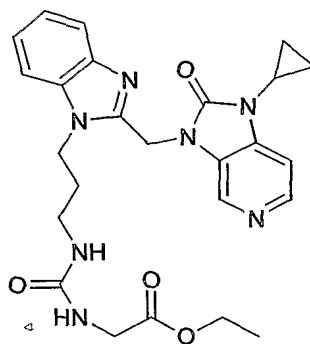
15



Example **56** was prepared according to the same procedure described for Example **50** using ethyl chloroformate.

- ^1H NMR (DMSO-d_6) δ 0.89-0.94 (m, 2 H), 1.03-1.09 (m, 2 H), 1.16 (t, $J = 7.1$ Hz, 3 H), 1.80-1.86 (m, 2 H), 2.98-3.03 (m, 1 H), 3.04-3.08 (m, 2 H), 4.00 (q, $J = 7.1$ Hz, 2 H), 4.35 (t, $J = 7.5$ Hz, 2 H), 5.39 (s, 2 H), 7.23-7.29 (m, 3 H), 7.29 (d, $J = 5.2$ Hz, 1 H), 7.57 (d, $J = 8.8$ Hz, 2 H), 8.25 (d, $J = 5.1$ Hz, 1 H), 8.40 (s, 1 H);
- 5 MS m/e 435 (MH^+).

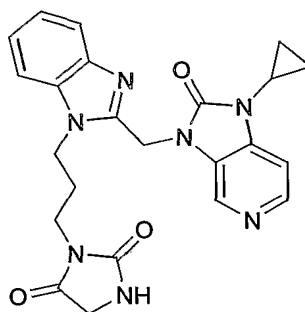
Example 57



10

- A solution of Example 49 (0.050 g, 0.14 mmol) in chloroform (2 mL) was treated with ethyl isocyanatoacetate (0.018 g, 0.14 mmol) and stirred for 15 minutes at room temperature. The mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with
- 15 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.080 g (96 % yield) of the trifluoroacetic acid salt of Example 57 as a glassy, colorless solid.

- ^1H NMR (DMSO-d_6) δ 0.98-1.02 (m, 2 H), 1.13-1.17 (m, 5 H), 1.91-1.97 (m, 2 H), 3.10-3.12 (m, 2 H), 3.15-3.18 (m, 1 H), 3.76 (s, 2 H), 4.04 (q, $J = 7.1$ Hz, 2 H),
- 20 4.39 (t, $J = 7.5$ Hz, 2 H), 5.55 (s, 2 H), 6.31 (bs, 1 H), 6.43 (bs, 1 H), 7.23 (t, $J = 7.6$ Hz, 1 H), 7.29-7.33 (m, 1 H), 7.56 (d, $J = 8.0$ Hz, 1 H), 7.66 (d, $J = 8.1$ Hz, 1 H), 7.83 (d, $J = 6.3$ Hz, 1 H), 8.62 (d, $J = 5.8$ Hz, 1 H), 8.83 (s, 1 H);
- MS m/e 492 (MH^+).

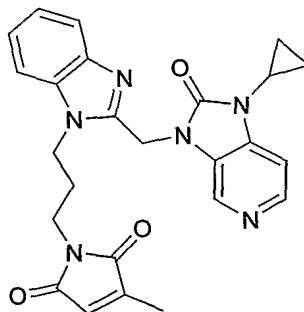
Example 58

5 Example **57** (0.061 g, 0.14 mmol) was dissolved in glacial acetic acid (2 mL) and the resulting solution was heated to 120 °C in a sealed tube for several hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 0.036 g (47 % yield) of the trifluoroacetic acid
10 salt of Example **58** as a glassy, colorless solid.

¹H NMR (DMSO-d₆) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.01-2.07 (m, 1 H), 3.13-3.18 (m, 2 H), 3.52 (t, J = 6.8 Hz, 2 H), 3.92 (s, 2 H), 4.38-4.43 (m, 2 H), 5.55 (s, 2 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.29-7.33 (m, 1 H), 7.56-7.59 (m, 1 H),
15 7.67 (d, J = 8.0 Hz, 1 H), 7.81-7.83 (m, 1 H), 8.09 (s, 1 H), 8.60-8.62 (m, 1 H), 8.80-8.82 (m, 1 H);
MS m/e 446 (MH⁺).

Example 59

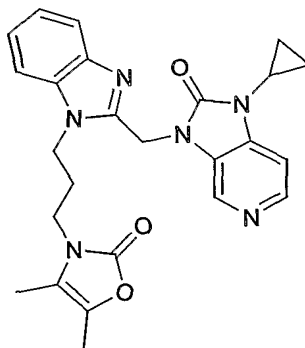
20



Example 49 (0.050 g, 0.14 mmol) was combined with citraconic anhydride (0.017 g, 0.15 mmol) and glacial acetic acid (2 mL). The resulting mixture was heated to 80 °C for 18 hours and then concentrated *in vacuo*. Purification by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) gave 0.052g (66 % yield) of the trifluoroacetic acid salt of Example 59 as a glassy, colorless solid.

¹H NMR (DMSO-d₆) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.00 (s, 3 H), 2.00-2.06 (m, 2 H), 3.12-3.17 (m, 1 H), 3.56 (t, J = 6.8 Hz, 2 H), 4.40 (t, J = 7.7 Hz, 2 H), 5.51 (s, 2 H), 6.62-6.63 (m, 1 H), 7.22 (t, J = 7.4 Hz, 1 H), 7.29 (t, J = 7.3 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 6.2 Hz, 1 H), 8.59 (d, J = 4.7 Hz, 1 H), 8.80 (s, 1 H); MS m/e 457 (MH⁺).

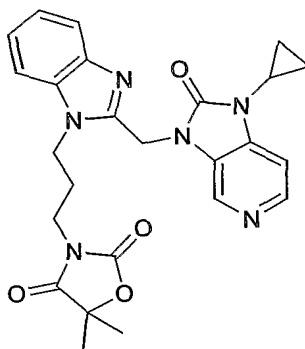
15

Example 60

Example 49 (0.050g, 0.14 mmol) was combined with 4,5-dimethyl-1,3-dioxo-2-one (0.016 g, 0.14 mmol), sodium bicarbonate (0.024 g, 0.14 mmol) and anhydrous DMF (2 mL), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 0.029 g (37 % yield) of the trifluoroacetic acid salt of Example 60 as a glassy, colorless solid.

¹H NMR (DMSO-d₆) δ 0.98-1.00 (m, 2 H), 1.13-1.17 (m, 2 H), 1.96 (s, 3 H), 2.00 (s, 3 H), 2.06-2.12 (m, 2 H), 3.13-3.18 (m, 1 H), 3.61 (t, J = 7.3 Hz, 2 H), 4.44 (t, J = 7.7 Hz, 2 H), 5.54 (s, 2 H), 7.22 (t, J = 7.3 Hz, 1 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.0 Hz, 1 H), 8.61 (d, J = 5.3 Hz, 1 H), 8.81 (s, 1 H);
MS m/e 459 (MH⁺).

Example 61

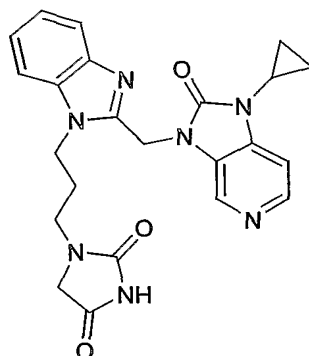


10

Example 49 (0.050 g, 0.14 mmol) was combined with methyl-2-hydroxyisobutyrate (0.018 g, 0.14 mmol), a catalytic amount of 50 % sodium methoxide in MeOH and diethyl carbonate (1 mL) in a sealed tube and the mixture was heated to 175 °C for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) to give 0.018 g (21 % yield) of the trifluoroacetic acid salt of Example 61 as a glassy, colorless solid.

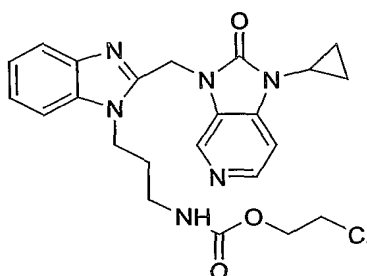
¹H NMR (DMSO-d₆) δ 0.99-1.01 (m, 2 H), 1.13-1.15 (m, 2 H), 1.52 (s, 6 H), 2.11 (t, J = 7.5 Hz, 2 H), 3.14-3.16 (m, 1 H), 3.60 (t, J = 6.9 Hz, 2 H), 4.46 (t, J = 7.7 Hz, 2 H), 5.54 (s, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.1 Hz, 1 H), 8.61 (s, 1 H), 8.81 (s, 1 H);
MS m/e 475 (MH⁺).

25

Example 62

- 5 Example 49 (0.050 g, 0.14 mmol) was combined with N-chloroacetyl urethane (0.024 g, 0.14 mmol), sodium bicarbonate (0.023g, 0.28 mmol) and anhydrous acetonitrile (2 mL) in a sealed tube. The mixture was heated to 140 °C for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90%
10 MeOH in H₂O with 0.1% TFA) to give 0.030 g (39 % yield) of the trifluoroacetic acid salt of Example 62 as a glassy, colorless solid.

- ¹H NMR (DMSO-d₆) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.00-2.06 (m, 2 H), 3.13-3.18 (m, 1 H), 3.41 (t, J = 6.8 Hz, 2 H), 4.00 (s, 2 H), 4.41 (t, J = 7.7 Hz, 2 H), 5.56 (s, 2 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.60 (d, J = 6.0 Hz, 1 H), 8.80 (s, 1 H), 10.77 (s, 1 H);
15 MS m/e 446 (MH⁺).

Example 63

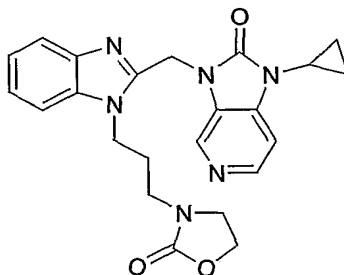
5 A mixture of Example 49 (100 mg, 0.27 mmol) and 2-bromoethylchloroformate (51.7 mg, 0.27 mmol) was stirred at room temperature for 18 hours. The reaction mixture was filtered to remove inorganic impurities and the solid was washed with MeOH. The MeOH solution was concentrated to give 126 mg (99% yield) of Example 63 as a hygroscopic solid.

10

^1H NMR (DMSO- d_6) δ 0.94 (bs, 2 H), 1.10 (d, J = 5.4 Hz, 2 H), 1.21 (d, J = 6.4 Hz, 2 H), 1.86-1.89 (m, 2 H), 3.09-3.11 (m, 1 H), 3.78-3.80 (m, 1 H), 3.85-3.87 (m, 1 H), 4.21-4.23 (m, 2 H), 4.35-4.37 (m, 2 H), 5.43 (s, 2 H), 7.18 (t, J = 7.7 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 7.46-7.50 (m, 2 H), 7.55-7.60 (m, 1 H), 8.37 (d, J = 5.0 Hz, 1 H), 8.54 (s, 1 H);

15

MS m/e 469 (MH^+).

Example 64

20

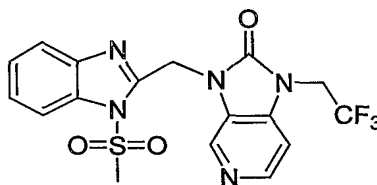
A mixture of Example 63 (70 mg, 0.149 mmol) and lithium bis(trimethylsilyl)amide (0.15 mL, 0.149 mmol) was stirred at reflux in dioxane

(15 mL) for 16 hours. The solvent was evaporated and the residue was diluted with EtOAc, washed with H₂O, dried over Na₂SO₄, and evaporated to give 41 mg (63% yield) of Example 64.

- 5 ¹H NMR (DMSO-d₆) δ 0.90-0.93 (m, 2 H), 1.01-1.09 (m, 2 H), 1.92-1.98 (m, 2 H), 2.98-3.03 (m, 1 H), 3.27 (t, J = 6.9 Hz, 2 H), 3.55 (t, J = 8.1 Hz, 2 H), 4.27 (t, J = 7.7 Hz, 2 H), 4.37 (t, J = 7.7 Hz, 2 H), 5.40 (s, 2 H), 7.17-7.20 (t, J = 7.4 Hz, 1 H), 7.22-7.29 (m, 2 H), 7.56-7.62 (m, 2 H), 8.25 (d, J = 5.3 Hz, 1 H), 8.42 (s, 1 H); MS m/e 416 (MH⁺).

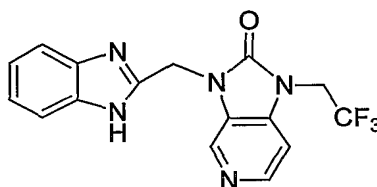
10

Example 65



- 15 MS m/e 426 (MH⁺).

Example 66



20

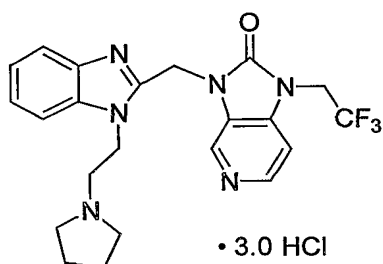
Example 65 was refluxed with hydrazine hydrate (5 mL) in MeOH (10 mL) for 1 hour. The solvent was evaporated and the oily residue was diluted with water and extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and evaporated to give 467 mg (29% yield) of Example 66.

25

^1H NMR (DMSO- d_6) δ 4.91 (q, J = 9.3 Hz, 2 H), 5.38 (s, 2 H), 7.12-7.21 (m, 2 H), 7.44 (d, J = 5.3 Hz, 1 H), 7.45-7.50 (m, 1 H), 7.51-7.58 (m, 1 H), 8.32 (d, J = 5.3 Hz, 1 H), 8.38 (s, 1 H), 12.60 (s, 1 H);

MS m/e 348 (MH^+).

5

Example 67

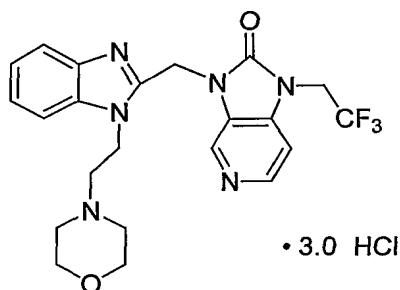
10 ^1H NMR (DMSO- d_6) δ 1.88-2.01 (m, 2 H), 2.01-2.13 (m, 2 H), 3.10-3.22 (m, 2 H), 3.58-3.65 (m, 2 H), 3.70-3.79 (m, 2 H), 4.90-4.99 (m, 2 H), 5.10-5.23 (m, 2 H), 5.95 (s, 2 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 6.1 Hz, 1 H), 8.76 (d, J = 6.4 Hz, 1 H), 9.18 (s, 1 H);

15 IR (KBr, cm^{-1}) 3416, 2927, 1754, 1653, 1627, 1518, 1462, 1264, 1168, 1121, 831, 755.

MS m/e 445 (MH^+).

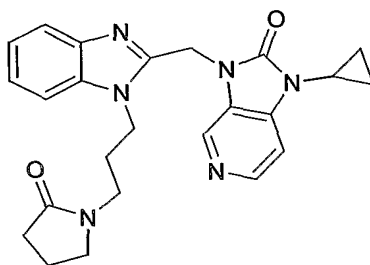
Example 68

20



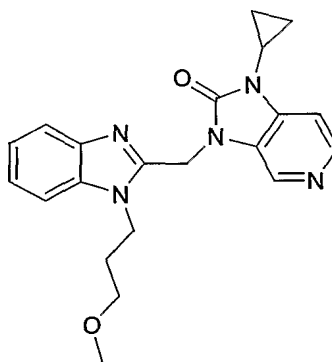
¹H NMR (DMSO-d₆) δ 3.19-3.31 (m, 2 H), 3.56-3.63 (m, 2 H), 3.65-3.74 (m, 2 H), 3.86-3.95 (m, 2 H), 4.00-4.09 (m, 2 H), 5.01 (t, J = 7.5 Hz, 2 H), 5.16 (q, J = 9.0 Hz, 2 H), 5.93 (s, 2 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.61 (d, J = 8.3 Hz, 1 H), 7.99 (d, J = 7.9 Hz, 1 H), 8.08 (d, J = 6.1 Hz, 1 H), 8.75 (d, J = 6.4 Hz, 1 H), 9.18 (s, 1 H);
IR (KBr, cm⁻¹) 3430, 1761, 1618, 1517, 1268, 1172, 823, 770;
MS m/e 461 (MH⁺).

Example 69



¹H NMR (DMSO-d₆) δ 1.03-1.08 (m, 2 H), 1.12-1.16 (m, 2 H), 2.01-2.17 (m, 2 H), 2.21-2.31 (m, 2 H), 2.31-2.41 (m, 2 H), 3.21-3.35 (m, 3 H), 3.40-50 (m, 1 H), 3.61-3.72 (m, 1 H), 4.45-4.51 (m, 2 H), 5.77(s, 2 H), 7.41-7.48 (m, 2 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.85-7.88 (m, 2 H), 8.64 (d, J = 6.7 Hz, 1 H), 8.95 (s, 1 H); MS m/e 430 (MH⁺).

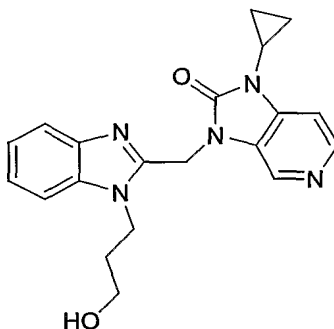
Example 70



^1H NMR (CDCl_3) δ 1.14 (q, $J = 7.5$ Hz, 2 H), 1.21 (q, $J = 6.4$ Hz, 2 H), 2.20-2.23 (m, 2 H), 3.07 (m, 1 H), 3.38 (s, 3 H), 3.38 (t, $J = 5.4$ Hz, 2 H), 4.56 (t, $J = 6.5$ Hz, 2 H), 5.85 (s, 2 H), 7.40 (t, $J = 7.6$ Hz, 1 H), 7.45 (t, $J = 7.7$ Hz, 1 H), 7.53-7.55 (m, 2 H), 7.88 (d, $J = 8.2$ Hz, 1 H), 8.38 (d, $J = 6.3$ Hz, 1 H), 8.92 (s, 1 H);

5 MS m/e 378 (MH^+).

Example 71



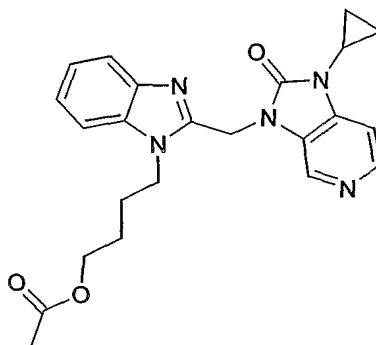
10

A solution of Example 70 (434 mg, 0.72 mmol) in CH_2Cl_2 (25 mL) was treated with boron tribromide (1M in CH_2Cl_2 , 7.2 mL, 7.2 mmol). The reaction mixture was stirred at room temperature for 40 minutes and then was quenched slowly with anhydrous MeOH. The solvent was evaporated and the residue was diluted with MeOH and evaporated two more times. Purification by flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) gave Example 71.

15

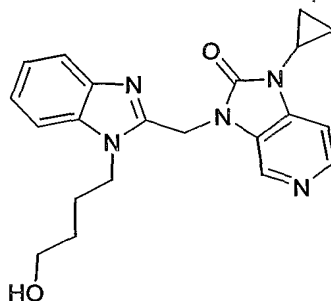
^1H NMR ($\text{DMSO}-d_6$) δ 1.07 (d, $J = 5.6$ Hz, 2 H), 1.83 (t, $J = 6.2$ Hz, 2 H), 2.99 (t, $J = 3.2$ Hz, 1 H), 3.17 (d, $J = 5.0$ Hz, 1 H), 3.40 (t, $J = 5.4$ Hz, 2 H), 4.40 (t, $J = 6.8$ Hz, 2 H), 4.75 (t, $J = 4.6$, 1 H), 5.42 (s, 2 H), 7.16 (t, $J = 7.5$ Hz, 1 H), 7.24 (t, $J = 7.6$ Hz, 1 H), 7.29 (d, $J = 4.8$ Hz, 1 H), 7.56 (d, $J = 8.1$ Hz, 2 H), 8.25 (s, 1 H), 8.38 (s, 1 H); MS m/e 364 (MH^+).

20

Example 72

- 5 ^1H NMR (CDCl_3) δ 0.99-1.03 (m, 2 H), 1.16-1.20 (m, 2 H), 1.65-1.69 (m, 2 H), 1.71-1.75 (m, 2 H), 2.00 (s, 3 H), 2.92-2.95 (m, 1 H), 4.03 (t, $J = 6.2$ Hz, 2 H), 4.35 (t, $J = 7.3$ Hz, 2 H), 5.37 (s, 2 H), 7.14 (d, $J = 5.0$ Hz, 1 H), 7.26-7.32 (m, 3 H), 7.56-7.77 (m, 1 H), 8.32 (d, $J = 5.4$ Hz, 1 H), 8.72 (s, 1 H); MS m/e 420 (MH^+).

10

Example 73

- Example 72 (1.0 g, 2.48 mmol) and K_2CO_3 (1.03 g, 7.44 mmol) were stirred together in MeOH (5 mL) at room temperature for 1.5 hours. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were washed with brine, dried over MgSO_4 , and evaporated. The product was then recrystallized from MeOH to give 650 mg (70% yield) of Example 73. Example 73 was converted to the HCl salt by treating a solution of 73 in MeOH with 4 N HCl in dioxane and then by evaporating the solvent.
- 15
- 20

¹H NMR (DMSO-d₆) δ 1.03-1.06 (m, 2 H), 1.12-1.16 (m, 2 H), 1.50-1.56 (m, 2 H), 1.89-1.83 (m, 2 H), 3.13-3.17 (m, 1 H), 3.46 (t, J = 6.3 Hz, 2 H), 4.46 (t, J = 7.5 Hz, 2 H), 5.70 (s, 2 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.81 (d, J = 6.4 Hz, 1 H), 8.61 (d, J = 6.4 Hz, 1 H), 8.93 (s, 1 H);

IR (KBr, cm⁻¹) 3350, 2907, 2443, 1736, 1516, 1421, 1172, 825;

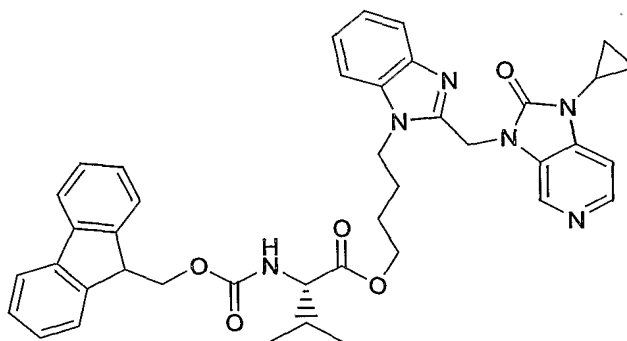
MS m/e 378 (MH⁺).

Anal. Calcd for C₂₉H₃₀N₄O₃•1.25 HCl: C, 59.63; H, 5.78; N, 16.56

Found: C, 59.52; H, 5.88; N, 16.57.

10

Example 74

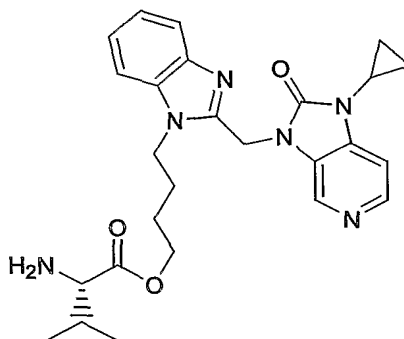


15 Fmoc-L-valine (0.690 g, 2.00 mmol) was combined with oxalyl chloride (0.508 g, 4.00 mmol) and dichloromethane (10 mL), and the resulting solution was stirred for 2 hours. The mixture was concentrated *in vacuo* to a yellow oil, which was then combined with Example 73 (0.252 g, 0.667 mmol) in dry CH₃CN (15 mL). The resulting mixture was stirred for 72 hours, then was diluted with

20 H₂O (5 mL) and was concentrated *in vacuo*. The mixture was redissolved in EtOAc (50 mL) and the solution was washed successively with saturated aqueous NaHCO₃ (3 x 10 mL) and brine (10 mL). The aqueous extracts were combined and back-extracted with EtOAc. The combined organic extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo*. Purification of the crude material

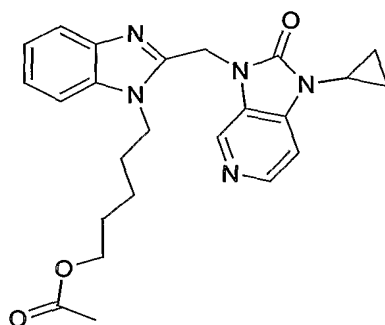
25 by flash chromatography (CH₂Cl₂:MeOH, 25:1) gave 410 mg of Example 74 as an off-white solid which was used immediately upon isolation.

Example 75

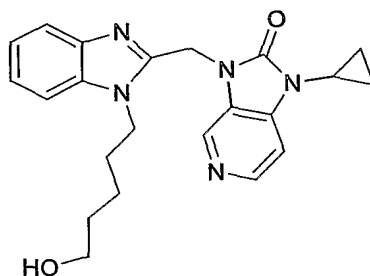


5 A solution of Example 74 (410 mg) and piperidine (4 mL) in DMF (15 mL) was stirred for 18 hours. The mixture was concentrated *in vacuo*. The crude solid was redissolved in CH₂Cl₂ and filtered to remove insolubles. Purification of the crude product by flash chromatography (gradient, CH₂Cl₂:MeOH, 20:1 to 10:1) gave a 184 mg of an 85:15 mixture of Examples 75 and 73. Repurification
10 by preparative HPLC gave 284 mg (52 % yield) of pure Example 75 as the tris-trifluoroacetic acid salt.

¹H NMR (DMSO) δ 0.93 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.99-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 1.74-1.78 (m, 2 H), 1.86-1.92 (m, 2 H), 2.11-2.17 (m, 1 H), 3.13-3.17 (m, 1 H), 3.93 (br s, 1 H), 4.20-4.31 (m, 2 H), 4.44 (t, J = 7.4 Hz, 2 H), 5.56 (s, 2 H), 7.23 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 7.30 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 6.3 Hz, 1 H), 8.37 (br s, 2 H), 8.62 (d, J = 5.7 Hz, 1 H), 8.83 (s, 1 H);
15 MS m/e 477 (MH⁺).

Example 76

- 5 ^1H NMR (DMSO- d_6) δ 0.89-0.93 (m, 2 H), 1.06-1.08 (m, 2 H), 1.31-1.34 (m, 2 H), 1.54-1.58 (m, 2 H), 1.58-1.66 (m, 2 H), 1.98 (s, 3 H), 2.97-3.00 (m, 1 H), 3.96 (t, $J = 6.6$ Hz, 2 H), 4.32 (t, $J = 7.5$ Hz, 1 H), 5.39 (s, 2 H), 7.16 (t, $J = 7.2$ Hz, 1 H), 7.24 (t, $J = 7.0$ Hz, 1 H), 7.29 (d, $J = 5.0$ Hz, 1 H), 7.58 (t, $J = 7.8$ Hz, 2 H), 8.22 (bs, 1 H), 8.42 (bs, 1 H);
- 10 MS m/e 433 (MH^+).

Example 77

15

Example 76 (115 mg, 0.27 mmol) in 1 N HCl (20 mL) was heated to reflux for 1 hour then concentrated. The oily residue was triturated with EtOAc/MeOH to give 106 mg (94% yield) of Example 77 106 mg (94% yield) as the HCl salt.

20

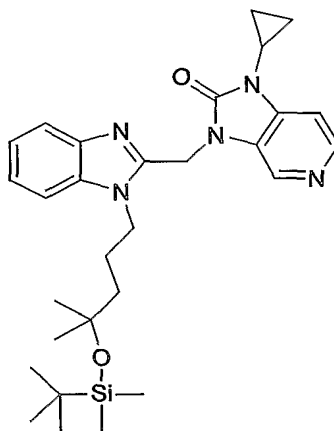
^1H NMR (DMSO- d_6) δ 1.04-1.10 (m, 2 H), 1.10-1.17 (m, 2 H), 1.42-1.53 (m, 4 H), 1.85-1.91 (m, 2 H), 3.13-3.17 (m, 1 H), 3.40-3.50 (m, 2 H), 4.51 (t, $J = 7.5$ Hz,

2 H), 5.82 (s, 2 H), 7.43-7.46 (m, 1 H), 7.46-7.52 (m, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 6.4 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 8.64 (d, J = 6.4 Hz, 1 H), 8.97 (s, 1 H);

MS m/e 391 (MH⁺).

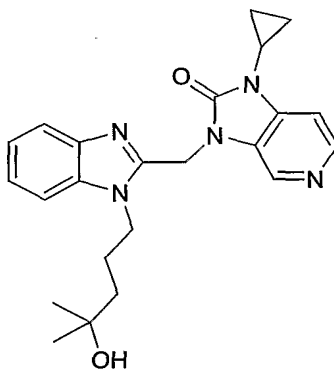
5

Example 78



10 Example 78 was prepared according to the general coupling procedure shown in Scheme I-C and was used immediately upon isolation.

Example 79



15

To a solution of Example 79 (86 mg, 0.17 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.25 mL, 0.25 mmol).

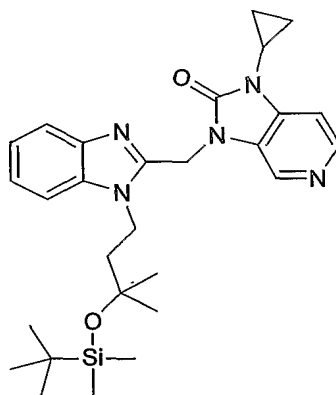
The reaction mixture was stirred at room temperature for 18 hours at which time more tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.50 mL, 0.50 mmol) was added and stirring was continued at room temperature for an additional 18 hours. Purification by flash column chromatography (CH₂Cl₂/MeOH, 9:1) gave

5 Example 79.

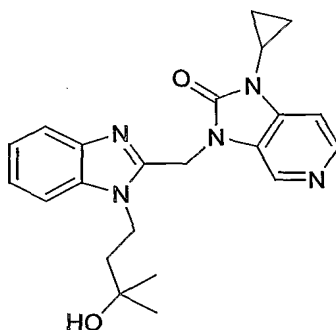
¹H NMR (CDCl₃) δ 0.94-0.97 (m, 2 H), 1.07 (s, 6 H), 1.09-1.11 (m, 2 H), 1.40 (t, J = 3.6 Hz, 2 H), 1.67-1.70 (m, 1 H), 2.86-2.87 (m, 1 H), 4.25 (t, J = 7.7 Hz, 2 H), 5.31 (s, 2 H), 7.05 (d, J = 5.3 Hz, 1 H), 7.18-7.21 (m, 2 H), 7.27 (t, J = 4.6 Hz, 1 H), 7.71 (t, J = 4.6 Hz, 1 H), 8.24 (d, J = 5.3 Hz, 1 H), 8.65 (s, 1 H);
10 IR (KBr, cm⁻¹) 3373, 2966, 1720, 1609, 1499, 1410, 913, 742;
MS m/e 406 (MH⁺).

Example 80

15



Example 80 was prepared according to the general coupling procedure shown in Scheme I-C and was used immediately upon isolation.

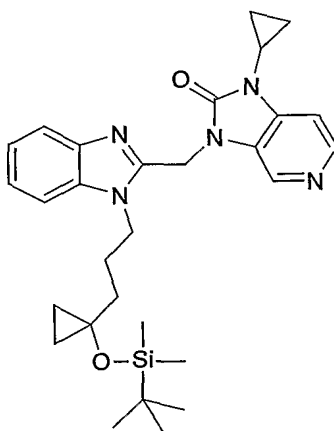
Example 81

5 Example 81 was prepared according to the same deprotection procedure as Example 79 from Example 80.

^1H NMR (CDCl_3) δ 1.02-1.04 (m, 2 H), 1.16 (q, $J = 6.9$ Hz, 2 H), 1.32 (s, 6 H),
1.81 (t, $J = 3.2$ Hz, H), 2.49 (s, 1 H), 2.93 (m, 1 H), 4.45 (t, $J = 3.4$ Hz, 2 H), 5.41
10 (s, 2 H), 7.14 (d, $J = 5.25$ Hz, 1 H), 7.27-7.30 (m, 2 H), 7.33 (dd, $J = 2.5, 3.5$ Hz, 1
H), 7.77 (dd, $J = 2.9, 3.1$ Hz, 1 H), 8.34 (d, $J = 5.3$, 1 H), 8.77 (s, 1 H);
MS m/e 392 (MH^+).

Example 82

15



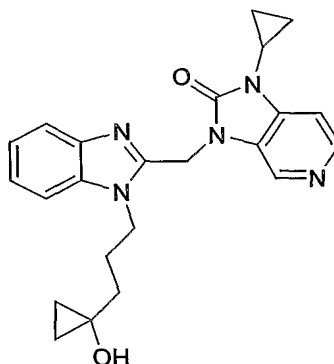
^1H NMR (CDCl_3) δ 0.03 (s, 6 H), 0.80-0.86 (m, 2 H), 0.89 (s, 9 H), 1.00-1.02 (m,
2 H), 1.15-1.17 (m, 2 H), 1.48-1.51 (m, 2 H), 1.77-1.86 (m, 2 H), 2.05 (t, $J = 7.4$

Hz, 2 H), 2.89-2.97 (m, 1 H), 4.29 (t, $J = 7.4$ Hz, 2 H), 5.35 (s, 2 H), 7.10 (d, $J = 5.2$ Hz, 1 H), 7.24-7.26 (m, 2 H), 7.31-7.33 (m, 1 H), 7.74-7.77 (m, 1 H), 8.31 (d, $J = 5.2$ Hz, 1 H), 8.69 (s, 1 H);

MS m/e 518 (MH^+).

5

Example 83



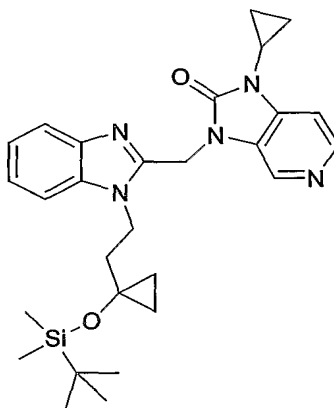
10 Example 83 was prepared from Example 82 according to the same deprotection procedure described for Example 79.

1H NMR ($DMSO-d_6$) δ 0.91-1.05 (m, 4 H), 1.13-1.22 (m, 2 H), 1.77-1.84 (m, 2 H), 2.27 (q, $J = 7.4$ Hz, 2 H), 2.39 (t, $J = 6.8$ Hz, 2 H), 2.89-2.95 (m, 1 H), 4.23 (t, $J = 7.7$ Hz, 2 H), 5.27 (s, 2 H), 7.03 (d, $J = 5.1$ Hz, 1 H), 7.24-7.31 (m, 2 H), 7.34 (dd, $J = 1.9, 6.4$ Hz, 1 H), 7.66 (dd, $J = 1.4, 7.1$ Hz, 1 H), 8.23 (d, $J = 5.2$ Hz, 1 H), 8.60 (s, 1 H);

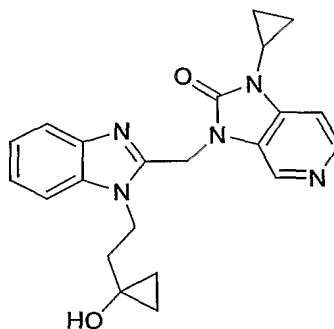
IR (KBr, cm^{-1}) 3392, 2938, 1721, 1609, 1499, 1410, 913, 743;

MS m/e 404 (MH^+).

15

Example 84

- 5 ^1H NMR (CDCl_3) δ 0.05 (t, $J = 5.8$ Hz, 2 H), 0.14 (s, 6 H), 0.63 (t, $J = 6.1$ Hz, 2 H), 0.90 (s, 9 H), 1.00-1.03 (m, 2 H), 1.13-1.17 (m, 2 H), 1.86 (t, $J = 6.6$ Hz, 2 H), 2.89-2.92 (m, 1 H), 4.61 (t, $J = 6.6$ Hz, 2 H), 5.42 (s, 2 H), 7.12 (d, $J = 4.9$ Hz, 1 H), 7.22-7.24 (m, 2 H), 7.38-7.40 (m, 1 H), 7.72-7.74 (m, 1 H), 8.32 (d, $J = 5.5$ Hz, 1 H), 8.66 (s, 1 H);
- 10 MS m/e 504 (MH^+).

Example 85

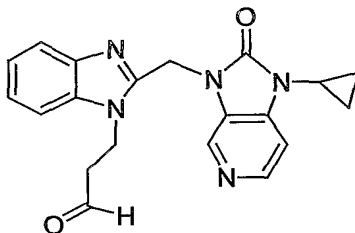
15

Example **85** was prepared from Example **84** according to the same deprotection procedure described for Example **79**.

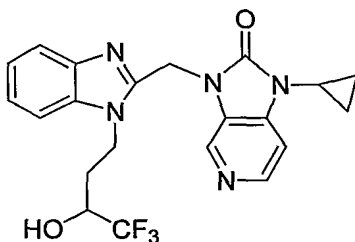
- ^1H NMR ($\text{DMSO}-d_6$) δ 0.10 (q, $J = 4.8$ Hz, 2 H), 0.49 (q, $J = 4.9$ Hz, 2 H), 0.90-0.94 (m, 2 H), 1.04-1.07 (m, 2 H), 1.85 (t, $J = 7.0$ Hz, 2 H), 2.99 (m, 1 H), 4.54 (t,
- 20

$J = 7.0$ Hz, 2 H), 5.42 (s, 1 H), 5.46 (s, 2 H), 7.16 (dt, $J = 1.0, 7.6$ Hz, 1 H), 7.23 (dt, $J = 1.0, 7.6$ Hz, 1 H), 7.28 (d, $J = 5.2$ Hz, 1 H), 7.54 (dd, $J = 8.0, 23.0$ Hz, 2 H), 8.25 (d, $J = 5.25$ Hz, 1 H), 8.39 (s, 1 H);
MS m/e 390 (MH^+).

5

Example 86

10 To a solution of oxalyl chloride (326 mg, 2.57 mmol) in CH_2Cl_2 (5 mL) cooled to -78 °C with a dry ice/acetone bath was added a solution of DMSO (268 mg, 3.42 mmol) in CH_2Cl_2 (10 mL) slowly over 15 minutes. After stirring for 10 minutes, a solution of Example 71 (622 mg, 1.71 mmol) in CH_2Cl_2 (5 mL) was slowly added to the reaction mixture. The reaction was monitored for completion
15 by thin layer chromatography and LC/MS. The solution became cloudy upon completion and the reaction was quenched at -78 °C by adding triethylamine (693 mg, 6.85 mmol). The solution became clear and was then warmed to room temperature. The reaction mixture was diluted with more CH_2Cl_2 , washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by flash column
20 chromatography (gradient, EtOAc/MeOH, 10:1 to 3:1) gave 185 mg (19% yield) of Example 86 which was used immediately upon isolation.

Example 87

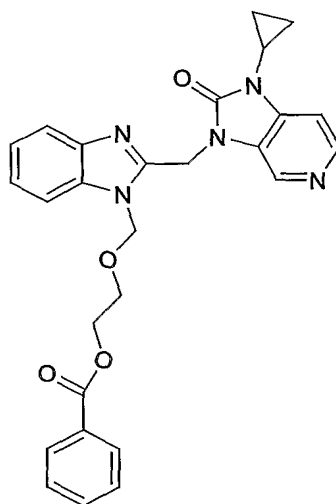
25

Example **87** was prepared according to the procedure described in *J. Med. Chem.*, **1996**, 39, 2411-2421 by Yu, K.-L. et al. using aldehyde **86**:

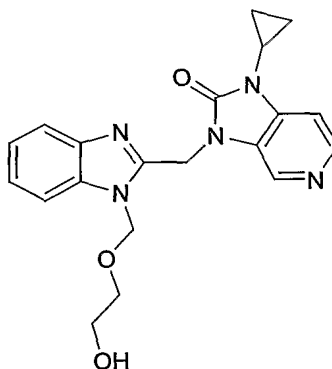
5 A fresh solution of anhydrous 1M tetrabutylammonium fluoride in THF was prepared according to the procedure described by Cox et al in *J. Organic Chemistry*, **1984**, 49, 3219-3220.

To a solution of Example **86** (150 mg, 0.42 mmol) in THF (10 mL) was added trimethyl(trifluoromethyl) silane (0.5M in THF, 1.25 mL, 0.62 mmol) followed by a catalytic amount of tetrabutylammonium fluoride (TBAF, 1M in THF, 8 μ L) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 hours and then warmed to room temperature. Additional trimethyl(trifluoromethyl) silane (0.5M in THF, 1.05 mL, 0.53 mmol) and TBAF (1M in THF, 8 μ L) were added to push the reaction toward completion. The reaction was quenched with excess TBAF (1M in THF, 2.88 mL, 2.88 mmol) and the reaction mixture was allowed to stir for 18 hours. The solvent was evaporated and the residue was purified by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) to give 106 mg (59% yield) of Example **87**.

20 ^1H NMR (CD_3OD) δ 0.98-1.07 (m, 2 H), 1.08-1.16 (m, 1 H), 1.89-1.97 (m, 1 H), 2.08-2.14 (m, 1 H), 2.99-3.04 (m, 2 H), 3.91-3.95 (m, 1 H), 4.53-4.63 (m, 2 H), 5.46-5.55 (m, 2 H), 7.25-7.28 (m, 1 H), 7.33 (dt, $J = 0.9, 7.8$ Hz, 1 H), 7.40 (d, $J = 5.5$ Hz, 1 H), 7.58 (d, $J = 8.1$ Hz, 2 H), 8.26 (d, $J = 5.4$ Hz, 1 H), 8.30 (s, 1 H); IR (KBr, cm^{-1}) 3422, 1723, 1613, 1504, 1412, 1173, 1131, 745;
25 MS m/e 432 (MH^+).

Example 88

- 5 ^1H NMR (CDCl_3) δ 0.92-0.95 (m, 2 H), 1.03-1.07 (m, 2 H), 2.81-2.85 (m, 1 H), 3.53 (t, $J = 4.8$ Hz, 2 H), 4.07 (t, $J = 4.8$ Hz, 2 H), 5.36 (s, 2 H), 5.69 (s, 2 H), 7.04 (d, $J = 5.5$ Hz, 1 H), 7.19-7.23 (m, 3 H), 7.33-7.39 (m, 3 H), 7.48-7.51 (m, 1 H), 7.70-7.72 (m, 1 H), 7.86 (d, $J = 8.3$ Hz, 1 H), 8.22 (d, $J = 5.2$ Hz, 1 H), 8.52 (s, 1 H);
- 10 MS m/e 484 (MH^+).

Example 89

15

To a solution of Example 88 (30.5 mg, 0.06 mmol) in MeOH (1 mL) was added ammonia (2 M in MeOH, 1 mL). The reaction mixture was stirred at room

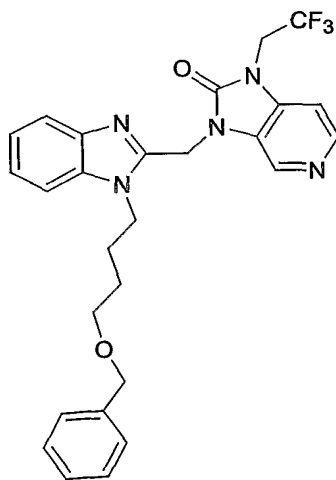
temperature for 16 hours. The solvent was concentrated. Purification by preparative HPLC (gradient, 10% MeOH in H₂O with 0.1% TFA to 90% MeOH in H₂O with 0.1% TFA) followed by treatment with excess 4 N HCl in dioxane gave Example 89 as the HCl salt.

5

¹H NMR (CD₃OD) δ 1.11-1.17 (m, 2 H), 1.21-1.26 (m, 2 H), 3.13-3.20 (m, 1 H), 3.59-3.66 (m, 2 H), 3.72-3.77 (m, 2 H), 5.98 (s, 2 H), 6.11 (s, 2 H), 7.62 (t, J = 7.4 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 4.2 Hz, 1 h), 8.04 (d, J = 8.0 Hz, 1 H), 8.58 (d, J = 3.9 Hz, 1 H), 8.89 (s, 1 H);

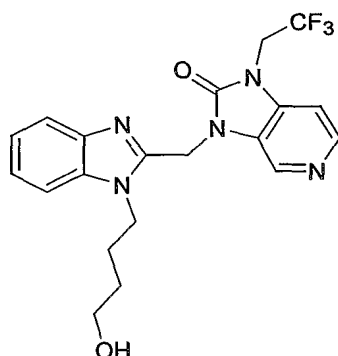
10 MS m/e 380 (MH⁺).

Example 90



15

MS m/e 510 (MH⁺).

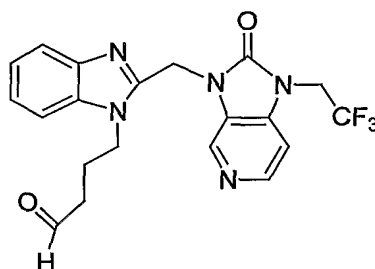
Example 91

5 Example 91 was prepared from Example 90 according to the same procedure described for Example 71.

^1H NMR (DMSO- d_6) δ 1.53-1.59 (m, 2 H), 1.87-1.92 (m, 2 H), 3.47 (t, J = 6.4 Hz, 2 H), 4.54 (t, J = 7.6 Hz, 2 H), 5.17 (q, J = 9.0 Hz, 2 H), 5.89 (s, 2 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.70 (d, J = 8.1 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 8.10 (d, J = 6.4 Hz, 1 H), 8.80 (d, J = 6.5 Hz, 1 H), 9.11 (s, 1 H).
10 MS m/e 420 (MH^+).

Example 92

15



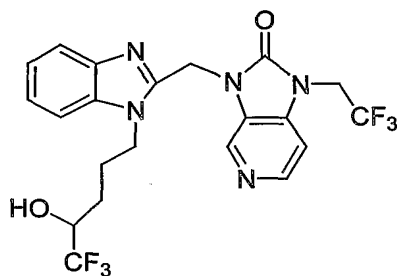
 Example 92 was prepared from Example 91 according to the same procedure described for Example 86.

20

^1H NMR (CDCl_3) δ 1.94-1.99 (m, 2 H), 2.59 (t, J = 6.7 Hz, 2 H), 4.31-4.35 (m, 2 H), 4.53 (q, J = 8.5 Hz, 2 H), 5.46 (s, 2 H), 7.07 (d, J = 6.4 Hz, 1 H), 7.27-7.34 (m,

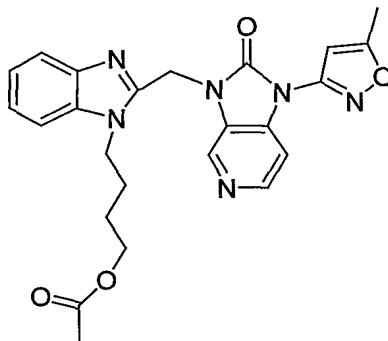
2 H), 7.44 (d, $J = 7.5$ Hz, 1 H), 8.78 (dd, $J = 0.9, 7.2$ Hz, 1 H), 8.39 (d, $J = 5.4$ Hz, 1 H), 8.85 (s, 1 H), 9.78 (s, 1 H);
MS m/e 418 (MH^+).

5

Example 93

Example 93 was prepared from Example 92 according to the same
10 procedure described for Example 87.

1H NMR (CD_3OD) δ 1.60-1.73 (m, 1 H), 1.78-1.90 (m, 1 H), 2.00-2.14 (m, 2 H),
3.96-4.01 (m, 1 H), 4.53 (t, $J = 7.8$ Hz, 2 H), 4.94 (q, $J = 8.9$ Hz, 2 H), 5.69 (s, 2 H),
7.34-7.44 (m, 2 H), 7.60 (d, $J = 7.8$ Hz, 1 H), 7.68 (d, $J = 7.5$ Hz, 1 H), 7.92 (d, $J =$
15 6.3 Hz, 1 H), 8.60 (d, $J = 5.7$ Hz, 1 H), 8.82 (s, 1 H);
MS m/e 488 (MH^+).

Example 94

20

^1H NMR (CDCl_3) δ 1.68-1.73 (m, 2 H), 1.74-1.80 (m, 2 H), 1.99 (s, 3 H), 2.54 (s, 3 H), 4.04 (t, $J = 6.3$ Hz, 2 H), 4.35 (t, $J = 7.5$ Hz, 2 H), 5.48 (s, 2 H), 6.97 (s, 1 H), 7.27-7.35 (m, 3 H), 7.78-7.80 (m, 1 H), 8.00 (d, $J = 5.4$ Hz, 1 H), 8.46 (d, $J = 5.4$ Hz, 1 H), 8.86 (s, 1 H);

5 IR (KBr, cm^{-1}) 3421, 1727, 1599, 1527, 1484, 1457, 1257, 751;

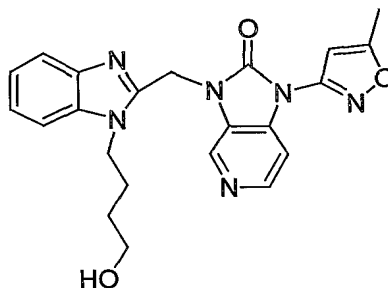
MS m/e 461 (MH^+);

Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_6\text{O}_4 \cdot 2.0 \text{ H}_2\text{O}$: C, 58.06; H, 5.68; N, 16.93

Found: C, 58.36; H, 5.55; N, 16.97.

10

Example 95



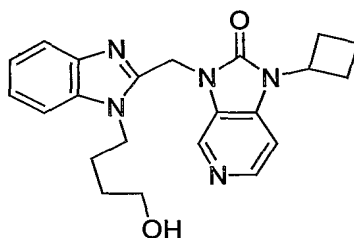
15 Example 95 was prepared from Example 94 according to the same procedure described for Example 73.

^1H NMR (CDCl_3) δ 1.60-1.66 (m, 2 H), 1.79-1.85 (m, 2 H), 3.65 (t, $J = 6.1$ Hz, 2 H), 4.35 (t, $J = 7.9$ Hz, 2 H), 5.50 (s, 2 H), 6.95 (s, 1 H), 7.28-7.36 (m, 3 H), 7.77-7.79 (m, 1 H), 8.00 (d, $J = 5.4$ Hz, 1 H), 8.45 (d, $J = 5.4$ Hz, 1 H), 8.87 (s, 1 H);

20 IR (KBr, cm^{-1}) 3309, 1728, 1602, 1528, 1483, 1452, 1385, 1171, 827, 739;

MS m/e 419 (MH^+).

Example 96

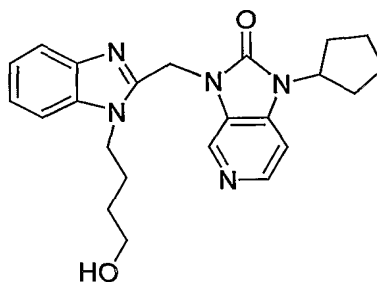


5 Example **96** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately by deprotection of the alcohol according to the same procedure described for Example **73**.

10 ¹H NMR (CDCl₃) δ 1.61-1.67 (m, 2 H), 1.79-1.85 (m, 2 H), 1.90-2.05 (m, 2 H), 2.43-2.49 (m, 2 H), 2.81-2.89 (m, 2 H), 3.68 (t, J=6.0 Hz, 2 H), 4.34 (t, J=7.8 Hz, 2 H), 4.85-4.92 (m, 1 H), 5.43 (s, 2 H), 7.22-7.35 (m, 4 H), 7.75-7.77 (m, 1 H), 8.33 (d, J= 5.5 Hz, 1 H), 8.82 (s, 1 H); MS m/e 392 (MH⁺);

15 Anal. Calcd for C₂₂H₂₅N₅O₂•0.5 H₂O: C, 65.98; H, 6.54; N, 17.49
 Found: C, 65.71; H, 6.62; N, 17.37.

Example 97



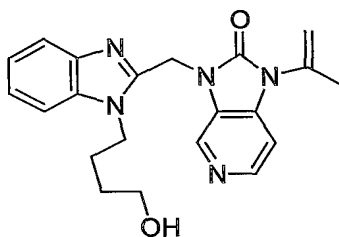
20

Example **97** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately

by deprotection of the alcohol according to the same procedure described for Example 73.

- ¹H NMR (CDCl₃) δ 1.61-1.67 (m, 2 H), 1.75-1.83 (m, 4 H), 1.95-2.02 (m, 2 H),
5 2.05-2.11 (m, 4 H), 3.68 (t, J = 6.0 Hz, 2 H), 4.35 (t, J = 7.9 Hz, 2 H), 4.82-4.89
(m, 1 H), 5.43 (s, 2 H), 7.04 (d, J = 5.5 Hz, 1 H), 7.22-7.30 (m, 2 H), 7.32-7.35
(m, 1 H), 7.76-7.78 (m, 1 H), 8.30 (d, J = 5.5 Hz, 1 H), 8.82 (s, 1 H);
IR (KBr, cm⁻¹) 3272, 2945, 2870, 1710, 1607, 1496, 1395, 742;
MS m/e 406 (MH⁺);
10 Anal. Calcd for C₂₃H₂₈N₅O₂: C, 67.95; H, 6.94; N, 17.22
Found: C, 67.78; H, 6.72; N, 16.92.

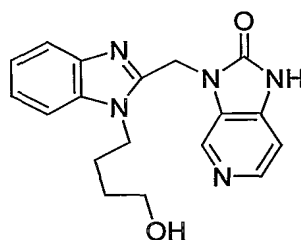
Example 98



15

Example 98 was prepared via synthesis of the acetate intermediate according to the same procedure described for Example 72 followed immediately by deprotection of the alcohol according to the same procedure described for
20 Example 73.

- ¹H NMR (DMSO-d₆) δ 1.43-1.48 (m, 2 H), 1.66-1.69 (m, 2 H), 2.18 (s, 3 H),
3.37-3.41 (m, 2 H), 4.35 (t, J = 7.3 Hz, 2 H), 4.47 (t, J = 5.1 Hz, 1 H), 5.25 (s, 1
H), 5.44 (s, 2 H), 5.46 (d, J = 1.0 Hz, 1 H), 7.17-7.27 (m, 3 H), 7.57-7.60 (m, 2 H),
25 8.25 (d, J = 5.2 Hz, 1 H), 8.48 (s, 1 H);
MS m/e 378 (MH⁺).

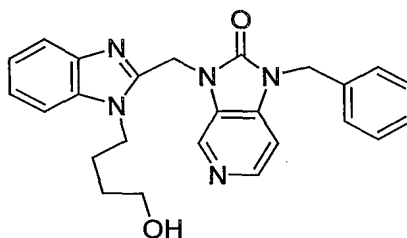
Example 99

5 Example 99 was prepared from Example 98 according to the same procedure described for Example 17.

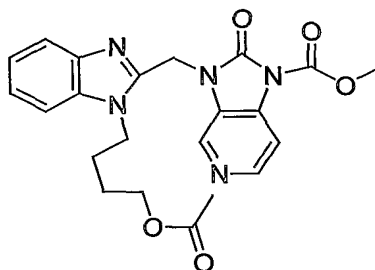
¹H NMR (DMSO-d₆) δ 1.44-1.48 (m, 2 H), 1.65-1.68 (m, 2 H), 3.38-3.42 (m, 2 H), 4.34 (t, J = 7.5 Hz, 2 H), 4.47 (t, J = 5.1 Hz, 1H), 5.38 (s, 1 H), 7.07 (d, J = 5.2
10 Hz, 1 H), 7.19 (t, J = 7.0 Hz, 1 H), 7.23 (t, J = 7.0 Hz, 1 H), 7.57 (t, J = 8.0 Hz, 1 H), 8.15 (d, J = 5.1 Hz, 1 H), 8.34 (s, 1 H), 11.59 (s, 1 H);
MS m/e 338 (MH⁺).

Example 100

15

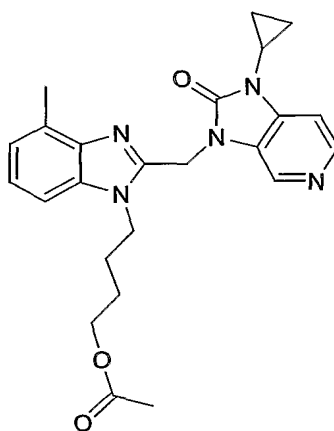


¹H NMR (CD₃OD) δ 1.54-1.60 (m, 2 H), 1.86-1.92 (m, 2 H), 3.52 (t, J = 6.2 Hz, 2 H), 4.45 (t, J = 7.7 Hz, 2 H), 5.20 (s, 1 H), 5.65 (d, J = 6.8 Hz, 2 H), 7.21-7.32 (m,
20 4 H), 7.34-7.37 (m, 3 H), 7.52-7.55 (m, 1 H), 7.63 (t, J = 8.4 Hz, 1 H), 8.37 (d, J = 6.5 Hz, 1 H), 8.68 (s, 1 H);
MS m/e 428 (MH⁺).

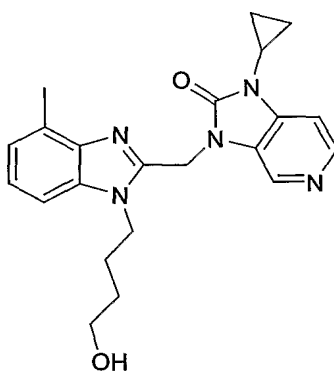
Example 101

5 To a solution of Example 99 (34 mg, 0.1 mmol) and 4-
dimethylaminopyridine (DMAP, 2.0 mg, 0.02 mmol) in pyridine (1 ml) was added
acetic anhydride (22 mg, 0.22 mmol) at room temperature. After stirring for 12
hours, the reaction mixture was diluted with EtOAc (10 ml) and washed twice
with H₂O and brine. The combined organic extracts were dried over MgSO₄, and
10 concentrated. The residue was purified by flash column chromatography
(CH₂Cl₂/MeOH, 20:1) to yield 35 mg (82%yield) of Example 101 as a white
solid.

¹H NMR (CDCl₃) δ 1.69-1.82 (m, 4 H), 2.00 (s, 3 H), 2.80 (s, 3 H), 4.06 (t, J = 6.2
15 Hz, 2 H), 4.34 (t, J = 6.6 Hz, 2 H), 5.39 (s, 2 H), 7.26-7.32 (m, 3 H), 7.75-7.78 (m,
1 H), 8.03 (d, J = 5.1 Hz, 1 H), 8.42 (d, J = 3.2 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 422 (MH⁺).

Example 102

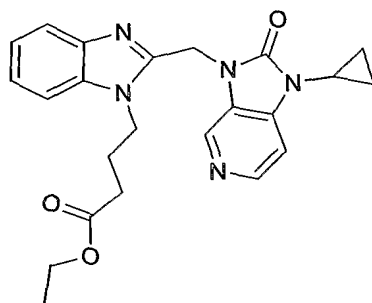
- 5 ¹H NMR (DMSO-d₆) δ 0.64-0.68 (m, 2 H), 0.81-0.86 (m, 2 H), 1.28-1.37 (m, 4 H), 1.72 (s, 3 H), 2.27 (s, 3 H), 2.73-2.77 (m, 1 H), 3.72 (t, J = 6.2 Hz, 2 H), 4.07 (t, J = 7.1 Hz, 2 H), 5.14 (s, 2 H), 6.76 (d, J = 7.3 Hz, 1 H), 6.90 (t, J = 7.7 Hz, 1 H), 7.03 (d, J = 5.25 Hz, 1 H), 7.13 (d, J = 8.1 Hz, 1 H), 8.00 (d, J = 5.25 Hz, 1 H), 8.23 (s, 1 H);
- 10 MS m/e 434 (MH⁺).

Example 103

15

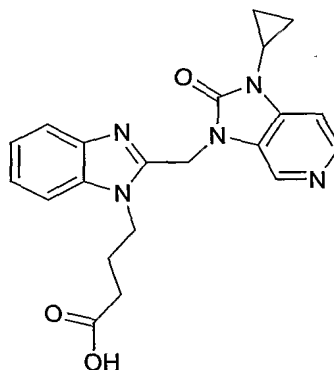
Example 103 was prepared from Example 102 according to the same procedure described for Example 73.

^1H NMR ($\text{DMSO}-d_6$) δ 0.90-0.95 (m, 2 H), 1.05-1.10 (m, 2 H), 1.35-1.41 (m, 2 H), 1.50-1.55 (m, 2 H), 2.51 (s, 3 H), 2.97-3.00 (m, 1 H), 4.27 (t, $J = 7.5$ Hz, 2 H), 4.43 (t, $J = 5.0$ Hz, 2 H), 5.38 (s, 2 H), 7.00 (d, $J = 7.2$ Hz, 1 H), 7.13 (t, $J = 7.7$ Hz, 1 H), 7.27 (d, $J = 5.2$ Hz, 1 H), 7.34 (d, $J = 8.1$ Hz, 1 H), 8.23 (d, $J = 5.2$ Hz, 1 H), 8.45 (s, 1 H);
MS m/e 392 (MH^+).

Example 104

10

^1H NMR (CDCl_3) δ 1.00-1.02 (m, 2 H), 1.14-1.18 (m, 2 H), 1.22 (t, $J = 7.1$ Hz, 3 H), 2.38 (t, $J = 7.15$ Hz, 2 H), 2.91-2.96 (m, 1 H), 4.10 (q, $J = 7.2$ Hz, 2 H), 4.38 (t, $J = 7.6$ Hz, 2 H), 5.37 (s, 2 H), 7.16 (d, $J = 5.4$ Hz, 1 H), 7.24-7.30 (m, 4 H), 7.39 (d, $J = 6.6$ Hz, 1 H), 7.75 (d, $J = 7.0$ Hz, 1 H), 8.33 (d, $J = 5.3$ Hz, 1 H), 8.71 (s, 1 H);
MS m/e 419 (MH^+).

Example 105

20

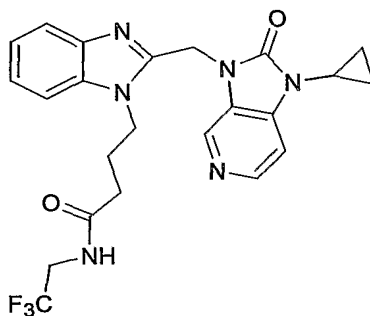
A mixture of Example **104** (346 mg, 0.83 mmol) and aqueous sodium hydroxide (1N, 4.1 mL, 4.13 mmol) were stirred in MeOH (5 mL) for 14 hours at room temperature. The mixture was neutralized with HCl followed by flash column chromatography to give Example **105**.

5

^1H NMR (CDCl_3) δ 1.13-1.16 (m, 2 H), 1.22-1.25 (m, 2 H), 2.36-2.41 (m, 4 H), 3.09-3.12 (m, 1 H), 4.56 (t, $J = 6.6$ Hz, 2 H), 5.91 (s, 2 H), 7.47-7.57 (m, 4 H), 7.93 (d, $J = 7.6$ Hz, 1 H), 8.37 (d, $J = 6.4$ Hz, 1 H), 9.17 (s, 1 H); MS m/e 392 (MH^+).

10

Example 106

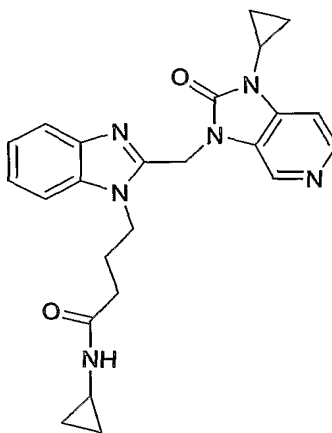


15 A solution of Example **105** (0.23 g, 0.50 mmol), 1-hydroxybenzotriazole hydrate (HOBT, 75 mg, 0.54 mmol), trifluoroethylamine hydrochloride (75 mg, 0.54 mmol), and N-methylmorpholine (0.21 g, 2.16 mmol) was stirred at room temperature for 30 minutes until a homogeneous solution resulted. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC, 103 mg, 0.54 mmol) was added and the mixture was stirred for 12 hours. The solution was
20 concentrated and the residue dissolved in EtOAc and washed with water and saturated NaHCO_3 , dried over MgSO_4 and concentrated to give 35 mg (18% yield) of Example **106** as a white solid.

25 ^1H NMR ($\text{DMSO}-d_6$) δ 0.89-0.93 (m, 2 H), 1.06-1.08 (m, 2 H), 1.86-1.89 (m, 2 H), 2.27-2.30 (m, 2 H), 2.98-3.00 (m, 1 H), 4.31-4.34 (m, 2 H), 5.40 (s, 2 H),

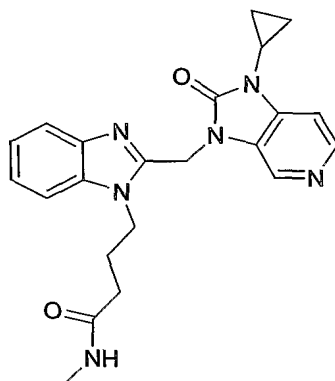
7.18-7.23 (m, 1 H), 7.25-7.29 (m, 2 H), 7.57-7.58 (m, 2 H) 8.25-8.26 (m, 1 H)
8.41 (s, 1 H), 8.57-8.60 (m, 1 H);
MS m/e 472 (MH⁺).

5

Example 107

Example **104** (100 mg, 0.24 mmol) in neat cyclopropylamine (1.22 g,
10 21.40 mmol) was heated at 105 °C in a sealed tube for 18 hours. The reaction
mixture was concentrated and the residue was purified by flash column
chromatography to give Example **107**.

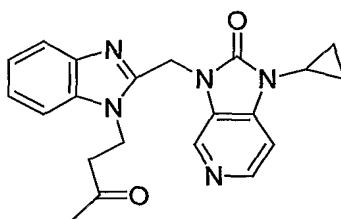
¹H NMR (CDCl₃) δ 0.45-0.48 (m, 2 H), 0.74-0.78 (m, 2 H), 0.98-1.03 (m, 2 H),
15 1.14-1.18 (m, 2 H), 1.99-2.04 (m, 2 H), 2.20 (t, J = 6.9 Hz, 2 H), 2.67-2.70 (m, 1
H), 2.92-2.96 (m, 1 H), 4.37 (t, J = 7.6 Hz, 2 H), 5.36 (s, 2 H), 7.14 (d, J = 5.2 Hz,
1 H), 7.24-7.29 (m, 2 H), 7.44 (d, J = 7.0 Hz, 1 H), 7.75 (d, J = 7.4 Hz, 1 H), 8.34
(d, J = 5.2 Hz, 1 H), 8.70 (s, 1 H);
MS m/e 431 (MH⁺).

Example 108

5 Example **104** (52 mg, 0.12 mmol) in methylamine (40% aqueous solution, 4 mL) was heated at 120 °C in a sealed tube for 18 hours. The solvent was evaporated and the residue purified by flash column chromatography to give Example **108** as a 2:1 mixture of cis/trans rotomers.

10 ^1H NMR (CDCl_3) δ 0.96-1.00 (m, 2 H), 1.08-1.14 (m, 2 H), 1.94-2.02 (m, 2 H), 2.19-2.23 (m, 2 H), 2.75 (d, J = 6.0 Hz, 3 H), 2.88-2.92 (m, 1 H), 4.29-4.36 (m, 2 H), 5.33, 5.34 (s, 2 H), 7.07, 7.10 (d, J = 6.5 Hz, 1 H), 7.11-7.27 (m, 2 H), 7.66-7.71 (m, 1 H), 8.25, 8.28 (d, J = 6.7 Hz, 1 H), 8.57, 8.63 (s, 1 H);
MS m/e 405 (MH^+).

15

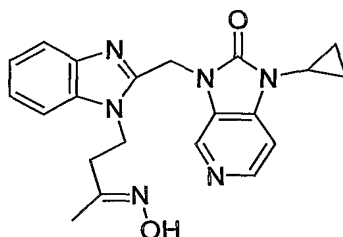
Example 109

20 A mixture of Example **47** (500 mg, 1.64 mmol) and methyl vinyl ketone (574 mg, 8.2 mmol) in EtOH (10 ml) was heated to reflux for 8 hours. After

cooling, the solid was collected by filtration to give 378 mg (61%) of Example 109 as a white solid.

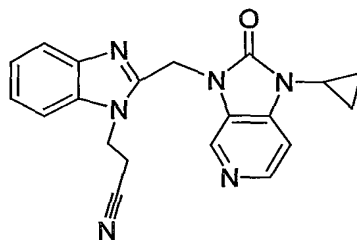
^1H NMR (CDCl_3) δ 1.01-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 2.10 (s, 3 H), 2.91-2.96 (m, 3 H), 4.60 (t, $J=6.4$ Hz, 2 H), 5.53 (s, 2 H), 7.17 (d, $J=5.4$ Hz, 1 H), 7.24-7.30 (m, 2 H), 7.32-7.34 (m, 1 H), 7.73-7.75 (m, 1 H), 8.34 (d, $J=5.4$ Hz, 1 H), 8.69 (s, 1 H);
MS m/e 376 (MH^+).

10

Example 110

A mixture of Example 109 (37 mg, 0.10 mmol) and hydroxylamine hydrochloride (7.6 mg, 0.11 mmol) in MeOH (2 ml) was heated to reflux for 2 hours, diluted with EtOAc (20 ml) and washed with aqueous saturated NaHCO_3 . The organic layer was separated, dried over MgSO_4 , and evaporated to give 34 mg (87% yield) of Example 110 as white solid.

^1H NMR (CDCl_3) δ 1.01-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 1.89 (s, 3 H), 2.64 (t, $J=6.5$ Hz, 2 H), 2.89-2.92 (m, 1 H), 4.58 (t, $J=6.6$ Hz, 2 H), 5.41 (s, 2 H), 7.12-7.31 (m, 4 H), 7.69-7.72 (m, 1 H), 8.29 (d, $J=4.8$ Hz, 1 H), 8.57 (s, 1 H);
MS m/e 391 (MH^+).

Example 111

5 ^1H NMR (CDCl_3) δ 1.03-1.07 (m, 2 H), 1.16-1.20 (m, 2 H), 2.86 (t, $J = 6.5$ Hz, 2 H), 2.93-2.97 (m, 1 H), 4.78 (t, $J = 6.5$ Hz, 2 H), 5.43 (s, 2 H), 7.18 (d, $J = 5.4$ Hz, 1 H), 7.30-7.36 (m, 3 H), 7.81-7.82 (m, 1 H), 8.36 (d, $J = 5.4$ Hz, 1 H), 8.84 (s, 1 H);

IR (KBr, cm^{-1}) 3405, 1709, 1605, 1500, 1466, 1455, 1411, 1179, 750;

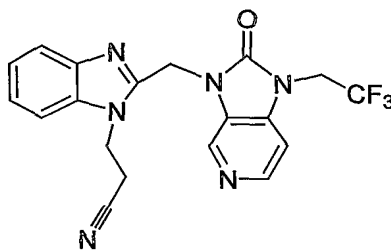
10 MS m/e 359 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_6\text{O} \cdot 0.5\text{H}_2\text{O}$: C, 65.38; H, 5.21; N, 22.87

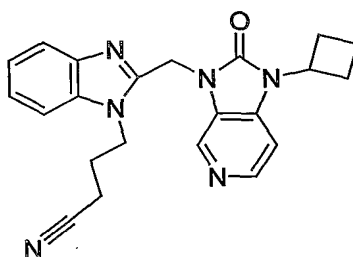
Found: C, 65.49; H, 5.09; N, 22.41.

Example 112

15



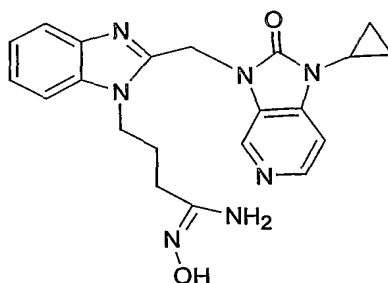
^1H NMR (CD_3OD) δ 3.11 (t, $J = 6.6$ Hz, 2 H), 4.72-4.82 (m, 4 H), 5.59 (s, 2 H), 7.28-7.38 (m, 3 H), 7.60-7.64 (m, 2 H), 8.29 (d, $J = 5.7$ Hz, 1 H), 8.53 (s, 1 H).

Example 113

5 ¹H NMR (CDCl₃) δ 1.90-2.10 (m, 4 H), 2.43-2.49 (m, 4 H), 2.80-2.89 (m, 2 H),
4.48 (t, J=7.4 Hz, 2 H), 4.84-4.90 (m, 1 H), 5.40 (s, 2 H), 7.21-7.38 (m, 4 H),
7.77-7.79 (m, 1 H), 8.34 (d, J= 5.5 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 387 (MH⁺);

Anal. Calcd for C₂₂H₂₂N₆O: C, 68.37; H, 5.73; N, 21.74

10 Found: C, 68.21; H, 5.83; N, 21.71.

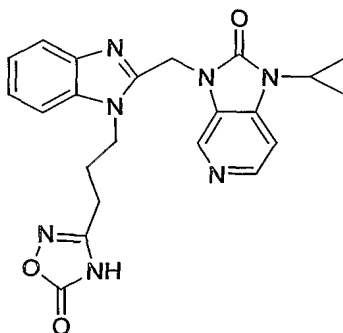
Example 114

15

A mixture of Example 26 (610 mg, 1.62 mmol), hydroxylamine hydrochloride (408 mg, 5.87 mmol) and potassium carbonate (450 mg, 3.24 mmol) were stirred in a EtOH and H₂O (2:1 ratio mixture, 60 mL) at 80 °C for 18 hours. The solvent was evaporated and the residue was diluted with H₂O to
20 dissolve inorganic salts. The white solid was filtered and dried under high vacuum to give 545 mg (83% yield) of Example 114 as a white solid.

¹H NMR (DMSO-d₆) δ 0.90-0.93 (m, 2 H), 1.05-1.07 (m, 2 H), 1.87-1.90 (m, 2 H), 2.06 (t, J = 7.5 Hz, 2 H), 3.00-3.02 (m, 1 H), 4.32 (t, J = 7.6 Hz, 2 H), 5.41 (s, 2 H), 5.46 (bs, 2 H), 7.17 (t, J = 7.3 Hz, 1 H), 7.24 (t, J = 7.3 Hz, 1 H), 7.29 (d, J = 5.2 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.40 (s, 1 H), 8.84 (s, 1 H).

Example 115



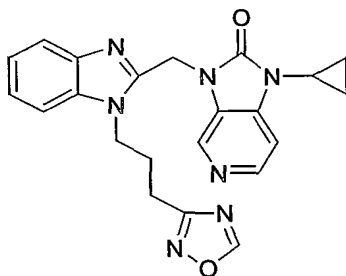
10

Example 114 (210 mg, 0.52 mmol) was treated with phosgene (20% in toluene, 2.56 g, 5.2 mmol) and heated to reflux for 12 hours. Additional phosgene (20% in toluene 2.56 g, 5.2 mmol) was added and the mixture heated to reflux for another 6 hours. The solution was concentrated to half volume and the white solid was isolated by filtration to give 138 mg (62% yield) of Example 115.

15

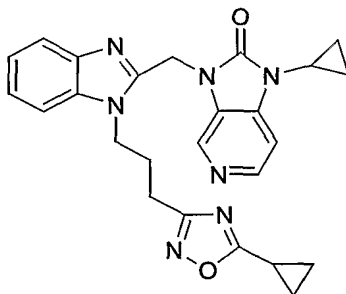
¹H NMR (DMSO-d₆) δ 1.05-1.05 (bs, 2 H), 1.15-1.16 (m, 2 H), 2.21-2.26 (m, 2 H), 2.71-2.75 (m, 2 H), 3.15-3.17 (m, 1 H), 4.51-4.58 (m, 2 H), 5.74-5.78 (m, 2 H), 7.37-7.40 (m, 1 H), 7.45-7.47 (m, 1 H), 7.63-7.66 (m, 1 H), 7.84-7.89 (m, 2 H), 8.64 (d, J = 6.4 Hz, 1 H), 8.92-8.95 (m, 1 H);
MS m/e 432 (MH⁺).

20

Example 116

5 A mixture of the Example 114 (100 mg, 0.24 mmol) was heated to reflux in triethylorthoformate (2.5 mL) for 12 hours. The solution was concentrated and the residue purified by preparative HPLC (C18, gradient 0-100% MeOH/H₂O with 0.1% trifluoroacetic acid). The product was treated with 4 N HCl in dioxane and concentrated to give 38 mg (35% yield) of the Example 116 as the
10 hydrochloride salt.

¹H NMR (DMSO-d₆) δ 0.97-1.02 (m, 2 H), 1.10-1.16 (m, 2 H), 2.25-2.35 (m, 2 H), 2.95-2.99 (m, 2 H), 3.14-3.16 (m, 1 H), 4.55-4.65 (m, 2 H), 5.77 (s, 2 H), 7.39-7.41 (m, 1 H), 7.46-7.48 (m, 1 H), 7.66-7.68 (m, 1 H), 7.84-7.90 (m, 2 H),
15 8.64 (d, J = 6.1 Hz, 1 H), 8.94 (s, 1 H), 9.57 (s, 1 H);
MS m/e 416 (MH⁺).

Example 117

20

A mixture of Example 114 (250 mg, 0.62 mmol) was heated to reflux with cyclopropanecarbonyl chloride (354 mg, 3.39 mmol) and pyridine (2 mL) for 12

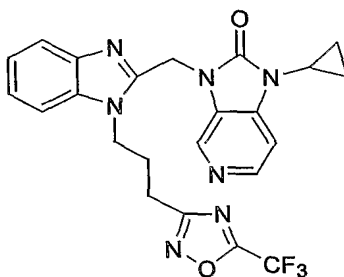
hours. The solution was concentrated and the residue purified by preparative HPLC (C18, gradient 0-100% MeOH/H₂O with 0.1% trifluoroacetic acid). The product was treated with 4N HCl in dioxane and concentrated to give 80 mg (28% yield) of Example 117 as the hydrochloride salt.

5

¹H NMR (DMSO-d₆) δ 1.04-1.06 (m, 4H), 1.13-1.15 (m, 2 H), 1.20-1.23 (m, 2 H), 2.21-2.31 (m, 2 H), 2.83-2.85 (m, 2 H), 3.11-3.19 (m, 1 H), 3.65-3.75 (m, 1 H), 4.55-4.57 (m, 2 H), 5.75 (s, 2 H), 7.35-7.42 (m, 1 H), 7.45-7.52 (m, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.83-7.85 (m, 2 H), 8.62 (d, J = 8.1 Hz, 1 H), 8.92 (s, 1 H);

10 MS m/e 456 (MH⁺).

Example 118

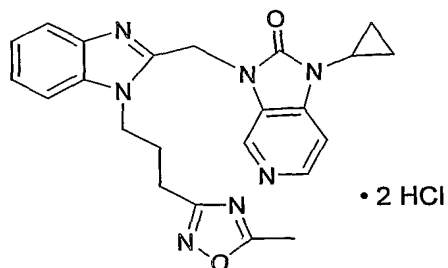


15

Example 118 was prepared according to the same procedure described for Example 117 using trifluoroacetic anhydride.

¹H NMR (DMSO-d₆) δ 1.02-1.05 (m, 2 H), 1.12-1.16 (m, 2 H), 2.31-2.34 (m, 2 H), 3.10 (t, J = 7.3 Hz, 2 H), 3.13-3.16 (m, 1 H), 4.59 (t, J = 7.6 Hz, 2 H), 5.74 (s, 2 H), 7.38 (t, J = 7.8 Hz, 1 H), 7.45 (t, J = 7.4 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 7.7 Hz, 1 H), 7.88 (d, J = 8.2 Hz, 1 H), 8.63 (d, J = 8.2 Hz, 1 H), 8.94 (s, 1 H);

20 MS m/e 483 (MH⁺).

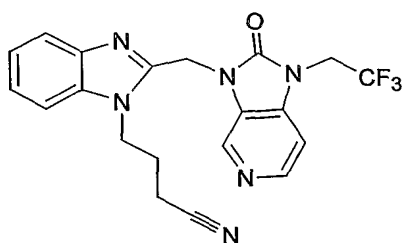
Example 119

5 Example 119 was prepared according to the same procedure described for Example 117 using acetic anhydride.

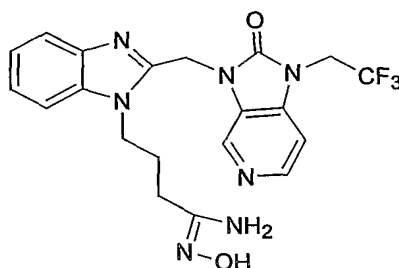
¹H NMR (DMSO-d₆) δ 1.01-1.05 (m, 2 H), 1.13-1.15 (m, 2 H), 2.24-2.28 (m, 2 H), 2.55 (s, 3 H), 2.85-2.88 (m, 1 H), 3.15-3.18 (m, 2 H), 4.55 (t, J = 7.4 Hz, 2 H),
10 5.71 (bs, 2 H), 7.29-7.38 (m, 1 H), 7.40-7.47 (m, 1 H), 7.64 (d, J = 7.4 Hz, 1 H), 7.80-7.86 (m, 2 H), 8.63 (d, J = 6.4 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 430 (MH⁺).

Example 120

15



¹H NMR (DMSO-d₆) δ 2.06-2.12 (m, 2 H), 2.63 (t, J = 7.3 Hz, 2 H), 4.42 (t, J =
7.5 Hz, 2 H), 4.92 (q, J = 9.3 Hz, 2 H), 5.51 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.27
20 (t, J = 7.5 Hz, 1 H), 7.45 (d, J = 5.2 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.62 (d, J =
8.2 Hz, 1 H), 8.33 (d, J = 5.5 Hz, 1 H), 8.51 (s, 1 H).

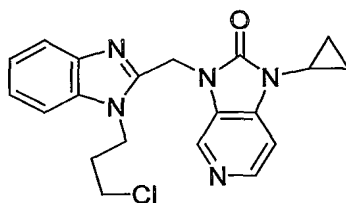
Example 121

5 Example 121 was prepared from Example 120 according to the same procedure as Example 114.

¹H NMR (DMSO-d₆) δ 1.91-1.98 (m, 2 H), 2.30 (t, J = 7.0 Hz, 2 H), 4.37 (t, J = 7.7 Hz, 2 H), 4.91 (q, J = 9.1 Hz, 2 H), 5.51 (s, 2 H), 7.15-7.18 (m, 1 H), 7.23-7.27 (m, 1 H), 7.44 (d, J = 5.2 Hz, 1 H), 7.55 (d, J = 7.9 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.06 (bs, 1 H), 8.31 (d, J = 5.2 Hz, 2 H), 8.46 (s, 1 H), 9.48 (s, 1 H);
 10 MS m/e 448 (MH⁺).

Example 122

15

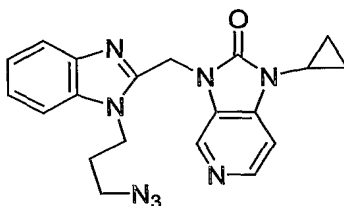


¹H NMR (CDCl₃) δ 1.00-1.06 (m, 2 H), 1.15-1.19 (m, 2 H), 2.14-2.19 (m, 2 H), 2.91-2.95 (m, 1 H), 3.55 (t, J=6.0 Hz, 2 H), 4.52 (t, J=6.7 Hz, 2 H), 5.40 (s, 2 H),
 20 7.14-7.15 (m, 1 H), 7.26-7.32 (m, 2 H), 7.39-7.40 (m, 1 H), 7.76-7.78 (m, 1 H), 8.34 (d, J=5.0 Hz, 1 H), 8.72 (s, 1 H);
 MS m/e 382 (MH⁺);

Anal. Calcd for C₂₀H₂₀ClN₅O: C, 62.90; H, 5.27; N, 18.34

Found: C, 62.58; H, 5.17; N, 18.18.

Example 123



5 A mixture of Example 122 (38 mg, 0.10 mmol) and sodium azide (20 mg, 0.30 mmol) in DMF (2 ml) was heated to 70 °C for 2 hours. The final solution was diluted with EtOAc (10 ml) and washed with H₂O (3 x 10 ml) and brine. The combined organic extracts were dried over MgSO₄, concentrated, and purified by flash chromatography, (gradient, CH₂Cl₂/MeOH, 40:1 to 20:1) to yield 33 mg
10 (85% yield) of Example 123 as a white solid.

¹H NMR (CDCl₃) δ 1.00-1.05 (m, 2 H), 1.13-1.19 (m, 2 H), 1.91-1.97 (m, 2 H), 2.90-2.94 (m, 1 H), 3.35 (t, J = 6.3 Hz, 2 H), 4.43 (t, J = 7.2 Hz, 2 H), 5.37 (s, 2 H), 7.12 (d, J = 5.2 Hz, 1 H), 7.26-7.30 (m, 2 H), 7.33-7.35 (m, 1 H), 7.77 (d, J =
15 7.2 Hz, 1 H), 8.32 (d, J = 5.0 Hz, 1 H), 8.72 (s, 1 H);

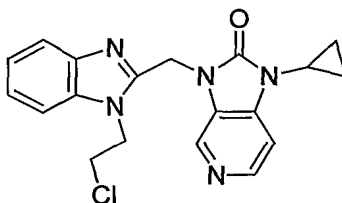
MS m/e 388 (MH⁺);

Anal. Calcd for C₂₀H₂₀N₈O: C, 61.84; H, 5.19; N, 28.84

Found: C, 61.59; H, 5.27; N, 28.50.

20

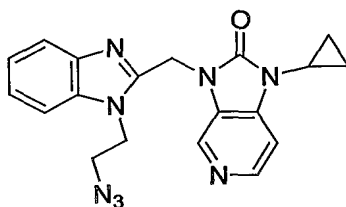
Example 124



¹H NMR (CDCl₃) δ 1.02-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 2.90-2.95 (m, 1 H),
25 3.77 (t, J = 6.0 Hz, 2 H), 4.76 (t, J = 6.1 Hz, 2 H), 5.44 (s, 2 H), 7.14 (d, J = 5.2

Hz, 1 H), 7.28-7.32 (m, 3 H), 7.78-7.80 (m, 1 H), 8.34 (d, J = 4.8 Hz, 1 H), 8.77 (s, 1 H);
MS m/e 368 (MH⁺).

5

Example 125

Example 125 was prepared from Example 124 according to the same
10 procedure described for Example 123.

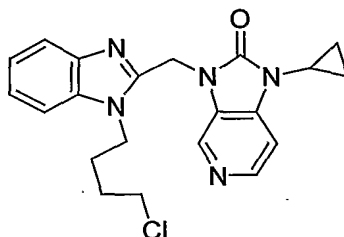
¹H NMR (CDCl₃) δ 1.01-1.06 (m, 2 H), 1.16-1.20 (m, 2 H), 2.92-2.96 (m, 1 H),
3.70 (t, J = 6.0 Hz, 2 H), 4.54 (t, J = 6.1 Hz, 2 H), 5.43 (s, 2 H), 7.15 (d, J = 5.2
15 Hz, 1 H), 7.29-7.32 (m, 3 H), 7.78-7.81 (m, 1 H), 8.34 (d, J = 4.8 Hz, 1 H), 8.79
(s, 1 H);

MS m/e 375 (MH⁺);

Anal. Calcd for C₁₉H₁₈N₈O • 0.25 H₂O: C, 60.23; H, 4.92; N, 29.57

Found: C, 60.30; H, 4.85; N, 29.44.

20

Example 126

¹H NMR (CDCl₃) δ 1.00-1.04 (m, 2 H), 1.16-1.20 (m, 2 H), 1.79-1.81 (m, 4 H),
25 2.92-2.96 (m, 1 H), 3.49-3.50 (m, 2 H), 4.35 (s, 2 H), 5.37 (s, 2 H), 7.13 (d, J=5.2

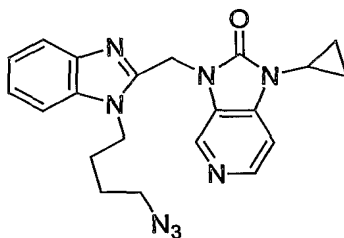
Hz, 1 H), 7.26-7.33 (m, 3 H), 7.76-7.79 (m, 1 H), 8.83 (d, J=5.2 Hz, 1 H), 8.72 (s, 1 H);

MS m/e 396 (MH⁺);

Anal. Calcd for C₂₁H₂₂ClN₅O • 0.20 H₂O: C, 63.14; H, 5.64; N, 17.53

Found: C, 62.74; H, 5.54; N, 17.57.

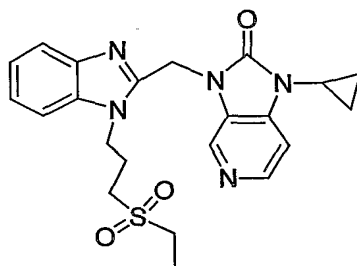
Example 127



Example 127 was prepared from Example 126 according to the same procedure described for Example 123.

¹H NMR (CDCl₃) δ 0.99-1.02 (m, 2 H), 1.15-1.19 (m, 2 H), 1.58-1.63 (m, 2 H), 1.69-1.75 (m, 2 H), 2.90-2.95 (m, 1 H), 3.27 (t, J = 6.5 Hz, 2 H), 4.32 (t, J = 7.3 Hz, 2 H), 5.35 (s, 2 H), 7.12 (d, J = 5.0 Hz, 1 H), 7.25-7.31 (m, 3 H), 7.76-7.77 (m, 1 H), 8.32 (d, J = 4.8 Hz, 1 H), 8.71 (s, 1 H);

MS m/e 403 (MH⁺).

Example 128

5 ^1H NMR (DMSO- d_6) δ 0.91-0.94 (m, 2 H), 1.04-1.09 (m, 2 H), 1.20 (t, $J = 7.5$ Hz, 3 H), 2.06-2.13 (m, 2 H), 2.98-3.02 (m, 1 H), 3.11 (q, $J = 7.5$ Hz, 2 H), 3.16-3.21 (m, 2 H), 4.86 (t, $J = 7.6$ Hz, 2 H), 5.42 (s, 2 H), 7.18-7.21 (m, 1 H), 7.26-7.30 (m, 2 H), 7.59 (d, $J = 8.0$ Hz, 1 H), 7.64 (d, $J = 8.1$ Hz, 1 H), 8.26 (d, $J = 5.3$ Hz, 1 H), 8.44 (s, 1 H);

10 IR (KBr, cm^{-1}) 3421, 1610, 1706, 1500, 1458, 1409, 1298, 1131, 751;

MS m/e 440 (MH^+);

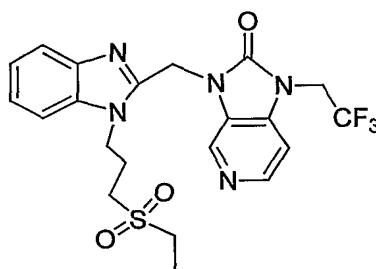
Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_3\text{S} \cdot 2 \text{H}_2\text{O}$:

C, 55.56; H, 6.15; N, 14.73

Found:

C, 55.29; H, 5.89; N, 14.59.

15

Example 129

20 ^1H NMR (DMSO- d_6) δ 1.21 (t, $J = 7.4$ Hz, 3 H), 2.14-2.16 (m, 2 H), 3.13 (q, $J = 7.4$ Hz, 2 H), 3.22 (t, $J = 7.5$ Hz, 2 H), 4.50 (t, $J = 7.5$ Hz, 2 H), 4.91 (q, $J = 9.3$ Hz, 2 H), 5.53 (s, 2 H), 7.19 (t, $J = 7.7$ Hz, 1 H), 7.28 (t, $J = 7.7$ Hz, 1 H), 7.46 (d, $J = 5.3$ Hz, 1 H), 7.57 (d, $J = 8.0$ Hz, 1 H), 7.65 (d, $J = 8.0$ Hz, 1 H), 8.33 (d, $J = 5.0$ Hz, 1 H), 8.52 (s, 1 H);

IR (KBr, cm^{-1}) 3430, 2945, 1726, 1615, 1500, 1411, 1266, 1170, 1125, 745;

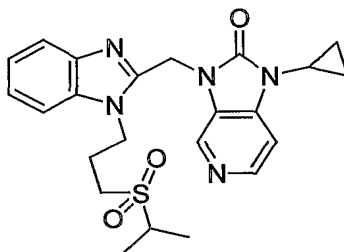
MS m/e 482 (MH^+);

Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_5\text{O}_3\text{S} \cdot 0.25 \text{H}_2\text{O}$: C, 51.90; H, 4.67; N, 14.41

Found: C, 51.69; H, 4.74; N, 14.17.

5

Example 130



10 ^1H NMR ($\text{DMSO}-d_6$) δ 0.92-0.93 (m, 2 H), 1.05-1.07 (m, 2 H), 1.23 (d, $J=6.8$ Hz, 6 H), 2.06-2.12 (m, 2 H), 2.98-3.02 (m, 1 H), 3.16-3.20 (m, 2 H), 3.28-3.30 (m, 1 H), 4.49 (t, $J=7.6$ Hz, 2 H), 5.42 (s, 2 H), 7.21 (t, $J=7.1$ Hz, 1 H), 7.26-7.30 (m, 2 H), 7.59 (d, $J=8.0$ Hz, 1 H), 7.64 (d, $J=8.0$ Hz, 1 H), 8.25 (d, $J=5.2$ Hz, 1 H), 8.44 (s, 1 H);

15 IR (KBr, cm^{-1}) 2926, 1720, 1604, 1498, 1471, 1420, 1267, 1126, 746;

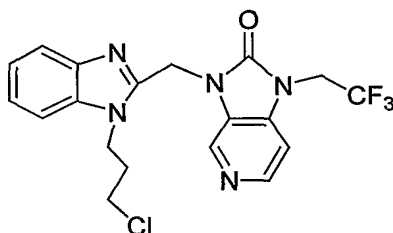
MS m/e 454 (MH^+);

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_3\text{S} \cdot 0.7 \text{H}_2\text{O}$: C, 59.26; H, 6.14; N, 15.02

Found: C, 59.58; H, 6.10; N, 14.63.

20

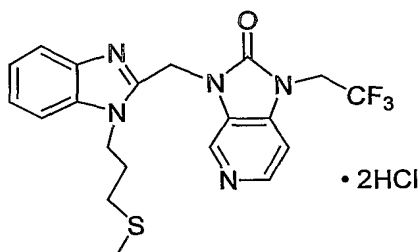
Example 131



^1H NMR (CDCl_3) δ 2.03-2.17 (m, 2 H), 3.53 (t, $J=6.2$ Hz, 2 H), 4.45-4.54 (m, 4 H), 5.44 (s, 2 H), 7.01 (d, $J=5.1$ Hz, 1 H), 7.24-7.32 (m, 2 H), 7.37-7.41 (m, 2 H),
25 7.73-7.78 (m, 1 H), 8.36 (d, $J=5.4$ Hz, 1 H), 8.79 (s, 1 H);

MS m/e 424 (MH^+).

Example 132



5

To a volume of DMF (10 mL) saturated with excess methanethiol at -78 °C was added sodium hydride (60% suspension in mineral oil, 56 mg, 1.39 mmol). The mixture was warmed to 0 °C and stirred for 30 minutes. The mixture was then added to a solution of Example 131 (394 mg, 0.93 mmol) in DMF (2 mL) and was stirred at 0 °C for 30 minutes. The solvent was evaporated under high vacuum. The residue was neutralized with concentrated HCl and the solvent was evaporated. The residue was diluted with CH₂Cl₂ and was washed with saturated aqueous NaHCO₃ and H₂O, dried over MgSO₄, and evaporated.

Purification by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 10:1) gave 374 mg (93% yield) of Example 132. Example 132 (200 mg, 0.46 mmol) was converted to the HCl salt by treating a solution of Example 132 in MeOH with excess 4N HCl in dioxane and then by evaporating the solvent to give 223 mg (96% yield).

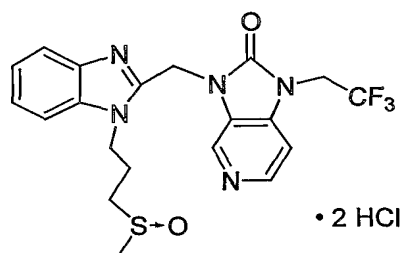
20

¹H NMR (CD₃OD) δ 2.14 (s, 3 H), 2.30-2.39 (m, 2 H), 2.70 (t, J = 6.6 Hz, 2 H), 4.78 (t, J = 7.4 Hz, 2 H), 5.01 (q, J = 8.7 Hz, 2 H), 6.05 (s, 2 H), 7.62-7.75 (m, 2 H), 7.76 (d, J = 7.5 Hz, 1 H), 7.99-8.04 (m, 2 H), 8.71 (d, J = 6.6 Hz, 1 H), 9.09 (s, 1 H);

IR (KBr, cm⁻¹) 3412, 2762, 1760, 1655, 1624, 1519, 1264, 1169, 1119, 834, 752; MS m/e 436 (MH^+).

25

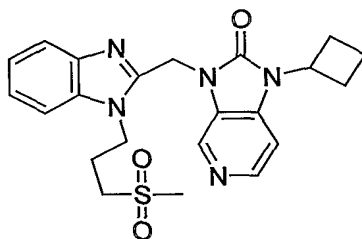
Example 133



5 A mixture of Example 132 (174 mg, 0.40 mmol) and sodium periodate (94 mg, 0.44 mmol) in H₂O (5 mL) was stirred at 0 °C. To this mixture was added DMF (2 mL) in order to dissolve the solids and the resulting solution was stirred at room temperature for 48 hours. The reaction mixture was diluted with CH₂Cl₂, washed with water, dried over MgSO₄ and evaporated. Purification by flash
10 column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) gave 145 mg (81% yield) of Example 133 which was converted to the HCl salt by treating a solution of Example 133 in MeOH with 4N HCl in dioxane and then by evaporating the solvent.

15 ¹H NMR (CD₃OD) δ 2.02-2.15 (m, 2 H), 2.53 (s, 3 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.43-4.56 (m, 4 H), 5.43 (s, 2 H), 7.02 (d, J = 5.1 Hz, 1 H), 7.26-7.31 (m, 2 H), 7.35-7.38 (m, 1 H), 7.74-7.77 (m, 1 H), 8.35 (d, J = 5.4 Hz, 1 H), 8.79 (s, 1 H); IR (KBr, cm⁻¹) 3412, 2854, 1760, 1656, 1624, 1519, 1264, 1169, 1120, 753; MS m/e 452 (MH⁺);

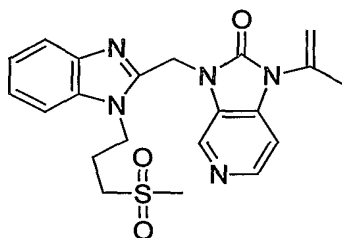
20	Anal. Calcd for $C_{20}H_{20}F_3N_5O_2S \cdot 2HCl \cdot H_2O$:	C, 44.29; H, 4.46; N, 12.91
	Found:	C, 44.08; H, 4.93; N, 11.54.

Example 135

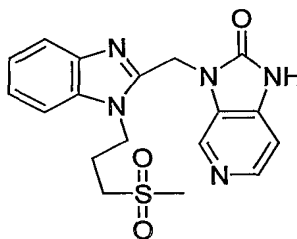
- 5 ^1H NMR (DMSO- d_6) δ 1.73-1.92 (m, 2 H), 2.13-2.16 (m, 2 H), 2.31-2.33 (m, 2 H), 2.79-2.83 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.7$ Hz, 2 H), 4.49 (t, $J = 7.4$ Hz, 2 H), 4.85-4.92 (m, 1 H), 5.44 (s, 2 H), 7.19-7.20 (m, 1 H), 7.26-7.27 (m, 1 H), 7.49 (d, $J = 5.3$ Hz, 1 H), 7.57 (d, $J = 8.0$ Hz, 1 H), 7.63 (d, $J = 8.05$ Hz, 1 H), 8.25 (d, $J = 5.3$ Hz, 1 H), 8.46 (s, 1 H);
- 10 MS m/e 440 (MH^+);
- Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_3\text{S}$: C, 60.11; H, 5.73; N, 15.93
- Found: C, 60.09; H, 5.76; N, 15.89.

Example 136

15



- ^1H NMR (DMSO- d_6) δ 2.12-2.18 (m, 5 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.6$ Hz, 2 H), 4.51 (t, $J = 7.6$ Hz, 2 H), 5.45-5.48 (m, 3 H), 7.19-7.28 (m, 3 H), 7.59 (d, $J = 8.0$ Hz, 1 H), 7.64 (d, $J = 8.1$ Hz, 1 H), 8.26 (d, $J = 5.3$ Hz, 1 H), 8.52 (s, 1 H);
- 20 MS m/e 426 (MH^+).

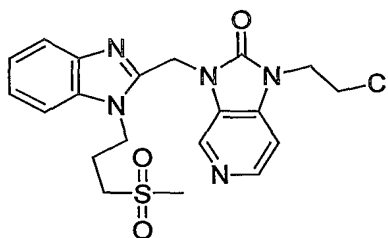
Example 137

5 Example 137 was prepared from Example 136 according to the same procedure described for Example 17.

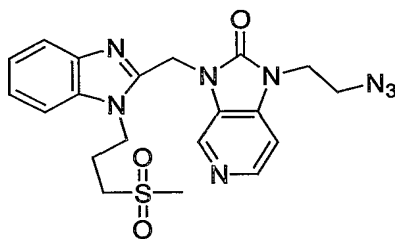
^1H NMR (DMSO-d_6) δ 2.12-2.16 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, $J = 7.6$ Hz, 2 H),
4.49 (t, $J = 7.6$ Hz, 2 H), 5.41 (s, 2 H), 7.08 (d, $J = 7.0$ Hz, 1 H), 7.17-7.20 (m, 1
10 H), 7.25-7.29 (m, 1 H), 7.58 (d, $J = 8.0$ Hz, 1 H), 7.63 (d, $J = 8.0$ Hz, 1 H), 8.17
(d, $J = 5.2$ Hz, 1 H), 8.39 (s, 1 H);
MS m/e 386 (MH^+).

Example 138

15



^1H NMR (CDCl_3) δ 2.16-2.22 (m, 2 H), 2.91 (s, 3 H), 3.09 (t, $J = 7.3$ Hz, 2 H),
3.88 (t, $J = 5.9$ Hz, 2 H), 4.26 (t, $J = 6.0$ Hz, 2 H), 4.51 (t, $J = 7.6$ Hz, 2 H), 5.44 (s,
20 2 H), 7.20 (d, $J = 5.3$ Hz, 1 H), 7.28-7.34 (m, 2 H), 7.37-7.39 (m, 1 H), 7.78-7.80
(m, 1 H), 8.36 (d, $J = 5.1$ Hz, 1 H), 8.78 (s, 1 H);
MS m/e 448 (MH^+).

Example 139

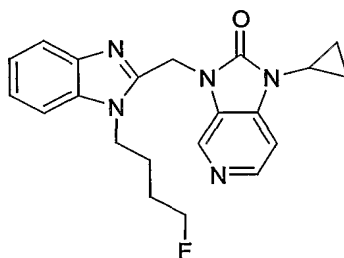
5 Example **139** was prepared from Example **138** according to the same procedure described for Example **123**.

^1H NMR (CDCl_3) δ 2.18-2.24 (m, 2 H), 2.91 (s, 3 H), 3.09 (t, $J = 7.3$ Hz, 2 H),
3.73 (t, $J = 5.9$ Hz, 2 H), 4.08 (t, $J = 6.0$ Hz, 2 H), 4.51 (t, $J = 7.6$ Hz, 2 H), 5.44 (s,
10 2 H), 7.07 (d, $J = 5.3$ Hz, 1 H), 7.26-7.33 (m, 2 H), 7.33-7.38 (m, 1 H), 7.77-7.79
(m, 1 H), 8.36 (d, $J = 5.1$ Hz, 1 H), 8.79 (s, 1 H);
MS m/e 455 (MH^+);

Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_3\text{S} \cdot 0.5 \text{H}_2\text{O}$: C, 51.83; H, 5.00; N, 24.17

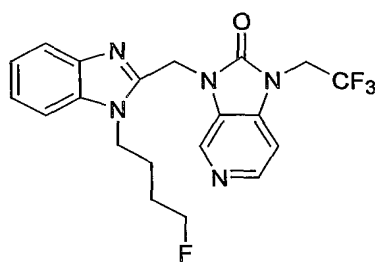
Found: C, 51.85; H, 4.82; N, 23.97.

15

Example 140

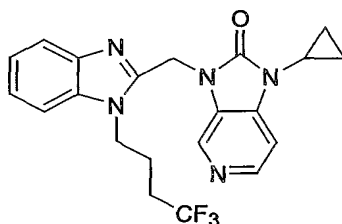
20 ^1H NMR ($\text{DMSO}-d_6$) δ 0.89-0.92 (m, 1 H), 1.06-1.08 (m, 1 H), 1.65-1.72 (m, 2
H), 2.96-2.99 (m, 1 H), 4.35-4.50 (m, 3 H), 5.40 (s, 2 H), 7.17-7.20 (m, 1 H),
7.24-7.29 (m, 2 H), 7.59 (d, $J = 8.2$ Hz, 2 H), 8.25 (d, $J = 5.1$ Hz, 1 H), 8.41 (s, 1
H);

MS m/e 380 (MH^+).

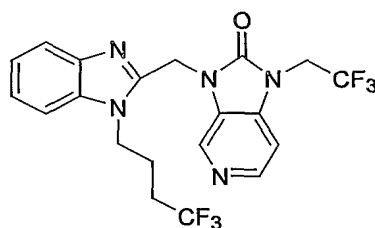
Example 141

- 5 ^1H NMR (DMSO- d_6) δ 1.67-1.77 (m, 4 H), 4.37-4.42 (m, 3 H), 4.49-4.51 (m, 1 H), 4.92 (q, $J = 9.2$ Hz, 2 H), 5.50 (s, 2 H), 7.18 (t, $J = 7.6$ Hz, 1 H), 7.26 (t, $J = 7.7$, 1 H), 7.44 (d, $J = 4.3$, 1 H), 7.57-7.61 (m, 2 H), 8.30-8.33 (bs, 1 H), 8.49-8.51 (bs, 1 H);
MS m/e 422 (MH^+).

10

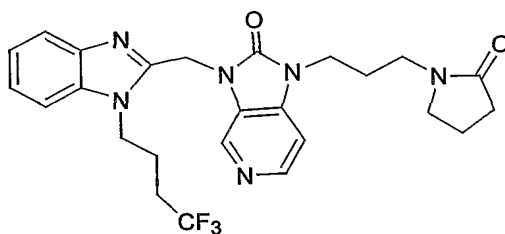
Example 142

- 15 ^1H NMR (DMSO- d_6) δ 1.03-1.04 (m, 2 H), 1.14-1.16 (m, 2 H), 2.06-2.08 (m, 2 H), 3.11-3.18 (m, 1 H), 4.52-4.55 (m, 4 H), 5.70 (s, 2 H), 7.34-7.39 (m, 1 H), 7.43-7.47 (m, 1 H), 7.63 (d, $J = 8.1$ Hz, 1 H), 7.84 (d, $J = 6.4$ Hz, 2 H), 8.63 (d, $J = 6.4$ Hz, 1 H), 8.92 (s, 1 H);
MS m/e 416 (MH^+).

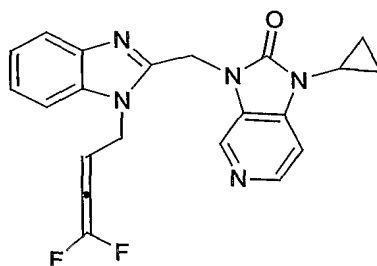
Example 143

- 5 ^1H NMR (DMSO- d_6) δ 1.84-1.87 (m, 2 H), 4.50-4.53 (m, 4 H), 5.14 (q, J = 9.0 Hz, 2 H), 5.74 (s, 2 H), 7.30-7.32 (m, 1 H), 7.37-7.40 (m, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.80 (d, J = 8.0, 1 H), 8.05 (d, J = 6.2 Hz, 1 H), 8.74 (d, J = 6.3 Hz, 1 H), 9.04 (s, 1 H);
MS m/e 458 (MH^+).

10

Example 144

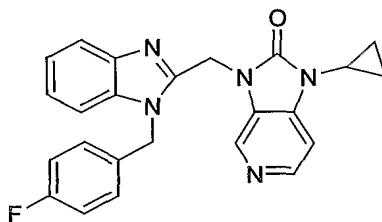
- 15 ^1H NMR (DMSO- d_6) δ 1.85-1.92 (m, 6 H), 2.18 (t, J = 8.1 Hz, 2 H), 2.36-2.41 (m, 2 H), 2.34 (t, J = 7.3 Hz, 2 H), 3.88 (t, J = 7.3 Hz, 2 H), 4.43 (t, J = 7.6 Hz, 2 H), 5.46 (s, 2 H), 7.19 (t, J = 7.0 Hz, 1 H), 7.27 (t, J = 7.0 Hz, 1 H), 7.38 (d, J = 5.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 7.9 Hz, 1 H), 8.26 (d, J = 5.2 Hz, 1 H), 8.46 (s, 1 H);
20 MS m/e 501 (MH^+).

Example 145

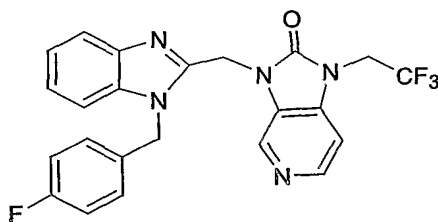
5 **Example 145** was prepared according to the general coupling procedure described in Scheme I-C with 4-bromo-1,1,2-trifluoro-1-butene which gave an elimination product.

¹H NMR (DMSO-d₆) δ 0.96-0.99 (m, 2 H), 1.14-1.16 (m, 2 H), 3.15-3.17 (m, 1
10 H), 5.53 (s, 2 H), 5.72 (d, J = 11.6 Hz, 1 H), 5.81 (d, J = 17.4 Hz, 1 H), 6.77-6.86 (m, 1 H), 7.34-7.42 (m, 2 H), 7.54 (d, J = 7.9 Hz, 1 H), 7.69 (d, J = 7.9 Hz, 1 H), 7.85 (d, J = 6.4 Hz, 1 H), 8.64 (d, J = 6.1 Hz, 1 H), 8.90 (s, 1 H); MS m/e 394 (MH⁺).

15

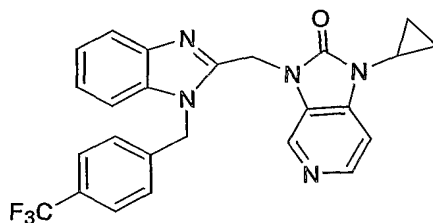
Example 146

¹H NMR (DMSO-d₆) δ 0.64-0.66 (m, 2 H), 0.97-0.98 (m, 2 H), 2.77-2.78 (m, 1 H),
20 5.40 (s, 2 H), 5.59 (s, 2 H), 6.77-6.81 (m, 2 H), 6.94 (t, J = 8.9 Hz, 2 H), 7.15 (d, J = 5.2 Hz, 1 H), 7.21-7.23 (m, 2 H), 7.40-7.42 (m, 1 H), 7.68-7.70 (m, 1 H), 8.20 (d, J = 5.2 Hz, 1 H), 8.31 (s, 1 H); MS m/e 413 (MH⁺).

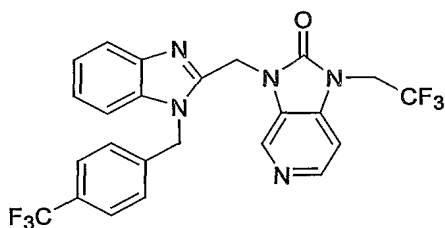
Example 147

- 5 ^1H NMR (DMSO- d_6) δ 4.74-4.79 (m, 2 H), 5.49 (s, 2 H), 5.60 (s, 2 H), 6.96-7.04 (m, 4 H), 7.17-7.25 (m, 2 H), 7.36 (d, J = 5.2 Hz, 1 H), 7.48 (d, J = 7.3 Hz, 1 H), 7.65 (d, J = 6.7 Hz, 1 H), 8.28 (d, J = 5.5 Hz, 1 H), 8.36 (s, 1 H);
MS m/e 456 (MH^+).

10

Example 148

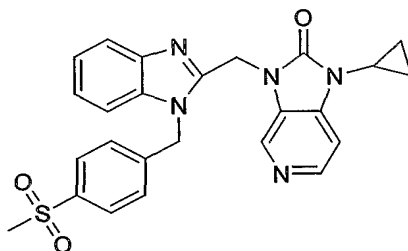
- 15 ^1H NMR (DMSO- d_6) δ 0.53-0.56 (m, 2 H), 0.92-0.96 (m, 2 H), 2.66-2.69 (m, 1 H), 5.41 (s, 2 H), 5.71 (s, 2 H), 6.83 (d, J = 8.2 Hz, 2 H), 7.06 (d, J = 5.2 Hz, 1 H), 7.23-7.25 (m, 2 H), 7.40-7.42 (m, 3 H), 7.72-7.74 (m, 1 H), 8.18 (d, J = 5.1 Hz, 1 H), 8.30 (s, 1 H);
MS m/e 464 (MH^+).

Example 149

- 5 ^1H NMR (DMSO- d_6) δ 4.68-4.70 (m, 2 H), 5.49 (s, 2 H), 5.74 (s, 2 H), 7.04 (d, J = 8.1 Hz, 2 H), 7.22-7.23 (m, 2H), 7.31 (d, J = 5.3 Hz, 1 H), 7.40-7.50 (m, 1H), 7.51 (d, J = 8.2 Hz, 2 H), 7.64-7.70 (m, 1 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.38 (s, 1 H);

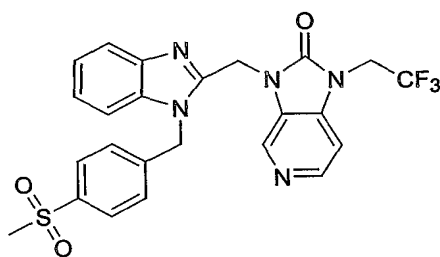
MS m/e 464 (MH^+).

10

Example 150

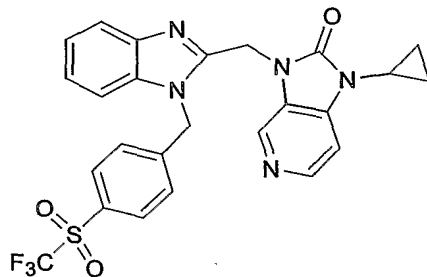
- 15 ^1H NMR (DMSO- d_6) δ 0.76-0.77 (m, 2 H), 1.05-1.07 (m, 2 H), 2.92-2.96 (m, 1 H), 3.56 (s, 3 H), 5.56 (s, 2 H), 5.81 (s, 2 H), 7.14 (d, J = 8.3 Hz, 2 H), 7.26-7.28 (m, 2 H), 7.47-7.49 (m, 1 H), 7.68-7.71 (m, 2 H), 7.77 (d, J = 8.4 Hz, 2 H), 8.58 (d, J = 6.4 Hz, 1 H), 8.72 (s, 1 H);

MS m/e 474 (MH^+).

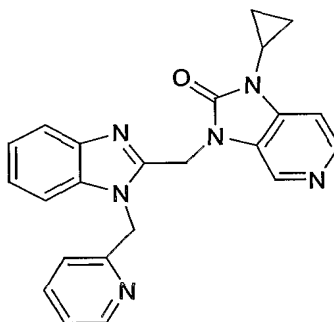
Example 151

- 5 ^1H NMR (DMSO-d_6) δ 3.20 (s, 3 H), 4.95-5.02 (m, 2 H), 5.66 (s, 2 H), 5.84 (s, 2 H), 5.56 (s, 2 H), 5.81 (s, 2 H), 7.26-7.29 (m, 2 H), 7.34 (d, $J = 8.3$ Hz, 2 H), 7.51-7.53 (m, 1 H), 7.64-7.66 (m, 1 H), 7.85 (d, $J = 8.4$ Hz, 2 H), 7.99 (d, $J = 6.3$ Hz, 1 H), 8.71 (d, $J = 6.4$ Hz, 1 H), 8.93 (s, 1 H);
MS m/e 516 (MH^+).

10

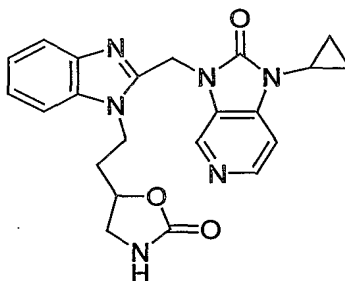
Example 152

- 15 ^1H NMR (DMSO-d_6) δ 0.78-0.81 (m, 2 H), 1.05-1.09 (m, 2 H), 2.95-2.98 (m, 1 H), 5.60 (s, 2 H), 5.95 (s, 2 H), 7.30 (dd, $J = 3.0, 6.1$ Hz, 2 H), 7.39 (d, $J = 8.6$ Hz, 2 H), 7.48-7.51 (m, 2 H), 7.71 (dd, $J = 3.0, 6.1$ Hz, 2 H), 7.73 (d, $J = 6.4$ Hz, 1 H), 8.04 (d, $J = 8.6$ Hz, 1 H), 8.60 (d, $J = 6.4$ Hz, 1 H), 8.82 (s, 1 H);
MS m/e 528 (MH^+).

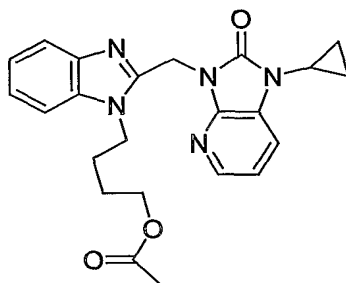
Example 153

- 5 ^1H NMR ($\text{DMSO}-d_6$) δ 0.68-0.71 (m, 2 H), 0.96-1.00 (m, 2 H), 2.79-2.82 (m, 1 H), 5.49 (s, 2 H), 5.69 (s, 2 H), 7.02 (d, $J = 7.9$ Hz, 1 H), 7.16-7.21 (m, 4 H), 7.43-7.45 (m, 1 H), 7.59-7.65 (m, 2 H), 8.21 (d, $J = 5.0$ Hz, 1 H), 8.24 (d, $J = 3.9$ Hz, 1 H), 8.35 (s, 1 H);

10

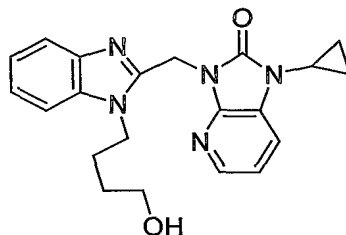
Example 154

- 15 ^1H NMR (CD_3OD) δ 1.16-1.20 (m, 2 H), 1.21-1.27 (m, 2 H), 2.44-2.48 (m, 1 H), 2.51-2.56 (m, 1 H), 3.18-3.22 (m, 1 H), 3.32-3.34 (m, 1 H), 3.74-3.78 (m, 1 H), 4.73-4.78 (m, 1 H), 4.81-4.89 (m, 2 H), 6.01 (d, 2 H), 7.63-7.67 (m, 1 H), 7.68-7.72 (m, 1 H), 7.79 (d, $J=8.2$ Hz, 1 H), 7.94 (d, $J=6.4$ Hz, 1 H), 8.02 (d, $J=8.3$ Hz, 1 H), 8.61 (d, $J=6.4$ Hz, 1 H), 8.96 (s, 1 H);
MS m/e 419 (MH^+).

Example 155

- 5 ^1H NMR (CDCl_3) δ 1.00-1.03 (m, 2 H), 1.08-1.12 (m, 2 H), 1.68-1.74 (m, 2 H), 1.84-1.90 (m, 2 H), 2.06 (s, 3 H), 3.47-3.51 (m, 2 H), 4.09 (t, $J=6.3$ Hz, 2 H), 4.46 (t, $J=7.5$ Hz, 2 H), 5.42 (s, 2 H), 6.99-7.01 (m, 1 H), 7.20-7.27 (m, 2 H), 7.33-7.37 (m, 2 H), 7.76 (d, $J=7.6$ Hz, 1 H), 8.06-8.07 (m, 1 H);
MS m/e 420 (MH^+).

10

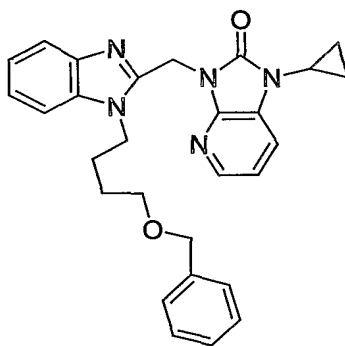
Example 156

- 15 Example 156 was prepared from Example 155 according to the same procedure described for Example 73.

- ^1H NMR (CD_3OD) δ 1.01-1.04 (m, 2 H), 1.13-1.68 (m, 2 H), 1.63-1.68 (m, 2 H), 1.94-2.01 (m, 2 H), 2.68 (s, 3 H), 3.01-3.04 (m, 1 H), 3.60 (t, $J=6.2$ Hz, 2 H), 4.69 (t, $J=7.9$ Hz, 2 H), 5.73 (s, 2 H), 7.19-7.22 (m, 1 H), 7.63-7.69 (m, 3 H), 7.74-7.76 (m, 1 H), 7.98 (d, $J=7.6$ Hz, 1 H), 8.03-8.04 (m, 1 H);
MS m/e 478 (MH^+);

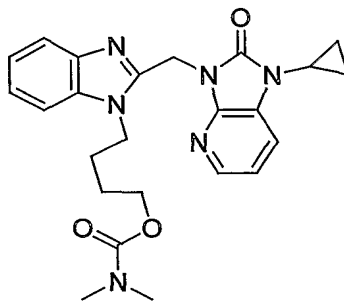
Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_2 \cdot \text{CH}_4\text{O}_3\text{S} \cdot 0.75 \text{H}_2\text{O}$: C, 54.21; H, 5.85; N, 14.22

Found: C, 54.25; H, 5.90; N, 14.38.

Example 157

- 5 ^1H NMR (CDCl_3) δ 0.98-1.01 (m, 2 H), 1.07-1.10 (m, 2 H), 1.65-1.71 (m, 2 H), 1.84-1.90 (m, 2 H), 2.86-2.90 (m, 1 H), 3.47-3.51 (m, 2 H), 4.43 (t, $J=7.6$ Hz, 2 H), 4.47 (s, 2 H), 5.37 (s, 2 H), 6.97-6.99 (m, 1 H), 7.18-7.33 (m, 9 H), 7.72-7.74 (m, 1 H), 8.03-8.06 (m, 1 H);
MS m/e 468 (MH^+).

10

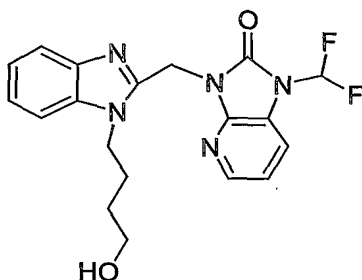
Example 158

- 15 To a suspension of Example **156** (52 mg, 0.14 mmol) and sodium hydride (6.6 mg, 0.16 mmol) in DMF (2 mL) was added N,N -dimethylcarbamoyl chloride (16.2 mg, 0.15 mmol) at 0°C . The resulting mixture was stirred at room temperature for 12 hours. The mixture was diluted with EtOAc and washed with water. The organic extracts were dried with MgSO_4 and evaporated. The residue
20 was purified by flash chromatography (gradient, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 40:1 to 20:1) to give 35 mg (56% yield) of Example **158** as a off-white solid.

^1H NMR (CDCl_3) δ 1.00-1.03 (m, 2 H), 1.08-1.12 (m, 2 H), 1.68-1.74 (m, 2 H), 1.84-1.90 (m, 2 H), 2.84 (s, 3 H), 2.90-2.93 (m, 4 H), 4.09 (t, $J=6.3$ Hz, 2 H), 4.46 (t, $J=7.5$ Hz, 2 H), 5.42 (s, 2 H), 6.99-7.01 (m, 1 H), 7.20-7.27 (m, 2 H), 7.33-7.37 (m, 2 H), 7.76 (d, $J=7.6$ Hz, 1 H), 8.06-8.07 (m, 1 H);

5 MS m/e 449 (MH^+).

Example 159



10

Example 159 was prepared via synthesis of the acetate intermediate according to the same procedure described for Example 72 followed immediately by deprotection of the alcohol according to the same procedure described for Example 73.

15

^1H NMR (d_6 -DMSO) δ 1.44-1.54 (m, 2 H), 1.77-1.86 (m, 2 H), 3.41 (t, $J = 6.3$ Hz, 2 H), 4.46 (t, $J = 7.2$ Hz, 2 H), 5.53 (s, 2 H), 7.21 (dd, $J = 5.3, 8.0$ Hz, 1 H), 7.28-7.40 (m, 2 H), 7.59 (d, $J = 7.8$ Hz, 1 H), 7.76 (d, $J = 7.8$ Hz, 2 H), 7.84 (t, $J = 57.6$ Hz, 1 H), 8.10 (d, $J = 4.8$ Hz, 1 H);

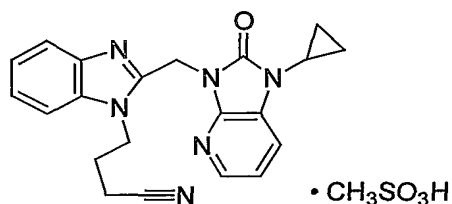
20 IR (KBr, cm^{-1}) 3275, 2941, 1751, 1623, 1606, 1466, 2503, 1031, 772, 746;

MS m/e 388 (MH^+);

Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{F}_2\text{N}_5\text{O}_2 \cdot 0.25 \text{H}_2\text{O}$: C, 58.23; H, 5.02; N, 17.87

Found: C, 58.42; H, 4.79; N, 17.64.

182

Example 160

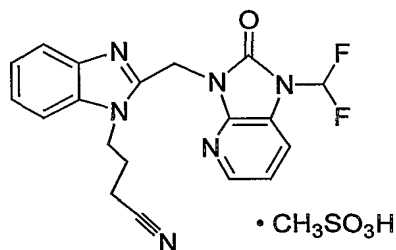
5 ¹H NMR (CD₃OD) δ 1.02-1.05 (m, 2 H), 1.11-1.17 (m, 2 H), 2.32-2.38 (m, 2 H), 2.68 (s, 3 H), 2.71 (t, J = 7.2 Hz, 2 H), 3.01-3.05 (m, 1 H), 5.79 (s, 2 H), 7.20-7.22 (m, 1 H), 7.64-7.76 (m, 4 H), 7.99-8.05 (m, 2 H);

MS m/e 373 (MH⁺);

Anal. Calcd for C₁₉H₁₈N₈O•1.0 H₂O•1.0 CH₄SO₃: C, 54.31; H, 5.39; N, 17.27

10

Found: C, 54.58; H, 5.37; N, 17.37.

Example 161

15

¹H NMR (CD₃OD) δ 2.37-2.40 (m, 2 H), 2.68 (s, 3 H), 2.73 (t, J = 7.3 Hz, 2 H), 4.82 (t, J = 7.6 Hz, 2 H), 5.80 (s, 2 H), 7.26-7.28 (m, 1 H), 7.62 (t, J = 58.0 Hz, 1 H), 7.65-7.79 (m, 4 H), 8.00 (d, J = 8.3 Hz, 1 H), 8.17 (dd, J = 1.3, 5.3 Hz, 1 H);

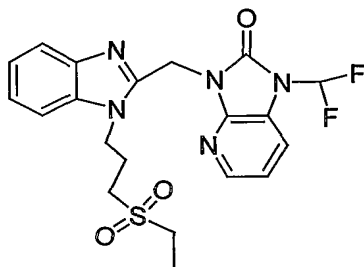
IR (KBr, cm⁻¹) 3449, 3064, 2953, 1758, 1466, 1410, 1230, 1156, 1048, 771, 551;

20 MS m/e 383 (MH⁺);

Anal. Calcd for C₁₉H₁₆F₂N₆O•0.5 H₂O•1.0 CH₃SO₃H:

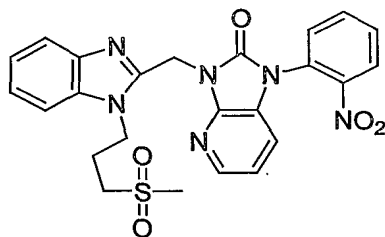
C, 49.28; H, 4.34; N, 17.24

Found: C, 49.36; H, 4.42; N, 16.95.

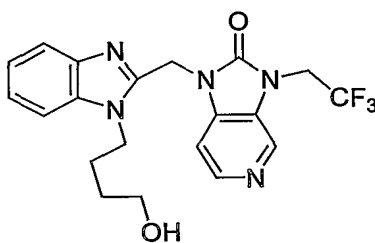
Example 162

- 5 ^1H NMR (CD_3OD) δ 1.35 (t, $J = 7.5$ Hz, 3 H), 2.50-2.57 (m, 2 H), 3.15 (q, $J = 7.5$ Hz, 2 H), 3.35 (t, $J = 7.2$ Hz, 2 H), 4.86 (t, $J = 7.2$ Hz, 2 H), 5.77 (s, 2 H), 7.24-7.27 (m, 1 H), 7.59-7.68 (m, 3 H), 7.62 (t, $J = 58.0$ Hz, 1 H), 7.71 (d, $J = 8.3$ Hz, 1 H), 7.78 (d, $J = 7.8$ Hz, 1 H), 7.98 (d, $J = 8.1$ Hz, 1 H), 8.16 (d, $J = 5.2$ Hz, 1 H); MS m/e 450 (MH^+).

10

Example 163

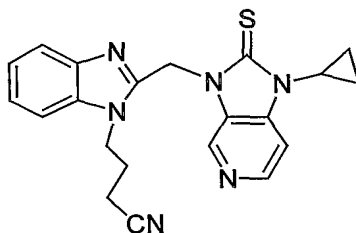
- 15 ^1H NMR ($\text{DMSO}-d_6$, 65°C) δ 2.81-2.34 (m, 2 H), 2.99 (s, 3 H), 3.28 (t, $J = 7.7$ Hz, 2 H), 4.57 (t, $J = 7.4$ Hz, 2 H), 5.50 (s, 2 H), 7.14-7.19 (m, 2 H), 7.25-7.27 (m, 1 H), 7.41 (d, $J = 8.0$ Hz, 1 H), 7.53 (d, $J = 7.9$ Hz, 1 H), 7.63 (d, $J = 8.1$ Hz, 1 H), 7.80-7.84 (m, 1 H), 7.91 (d, $J = 7.6$ Hz, 1 H), 7.98-8.02 (m, 1 H), 8.09 (d, $J = 5.0$ Hz, 1 H), 8.25-8.27 (m, 1 H);
- 20 MS m/e 507 (MH^+).

Example 164

5 Example 164 was prepared via synthesis of the acetate intermediate according to the same procedure described for Example 72 followed immediately by deprotection of the alcohol according to the same procedure described for Example 73.

10 ^1H NMR (CDCl_3) δ 1.60-1.65 (m, 2 H), 1.73-1.80 (m, 2 H), 3.64-3.70 (m, 2 H), 4.33 (t, $J=8.0$ Hz, 2 H), 4.53-4.60 (m, 2 H), 5.44 (s, 2 H), 7.24-7.37 (m, 3 H), 7.60 (d, $J=5.3$ Hz, 1 H), 7.77-7.81 (m, 1 H), 8.35-8.38 (m, 2 H);
MS m/e 420 (MH^+).

15

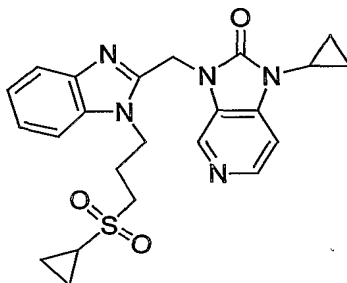
Example 165

20 A mixture of Example 26 (100 mg, 0.27 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, 130 mg, 0.32 mmol) in a mixture of toluene and dioxane (9:1 ratio, 10 mL) was heated in a sealed tube at 130 $^{\circ}\text{C}$ for 15 hours. The solvents were removed *in vacuo* and the residue was suspended in H_2O and extracted with CH_2Cl_2 . The organic phase was washed with brine, dried over MgSO_4 and evaporated. The
25 residue was purified by preparative TLC (5% MeOH in CH_2Cl_2), followed by

trituration from Et₂O to give 5 mg (5 % yield) of Example 165 as an off white solid.

¹H NMR (DMSO-d₆) δ 1.05-1.10 (m, 2 H), 1.21-1.25 (m, 2 H), 2.07-2.15 (m, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 3.23-3.26 (m, 1 H), 4.49 (t, J = 7.5 Hz, 2 H), 5.90 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.9 Hz, 1 H), 7.59 (d, J = 5.5 Hz, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 8.42 (d, J = 5.5 Hz, 1 H), 8.76 (s, 1 H);
MS m/e 389 (MH⁺).

10

Example 166

¹H NMR (CDCl₃) δ 1.00-1.07 (m, 4 H), 1.15-1.18 (m, 2 H), 1.16-1.23 (m, 2 H), 2.20-2.26 (m, 2 H), 2.32-2.38 (m, 1 H), 2.96-2.30 (m, 1 H), 3.09 (t, J = 7.2 Hz, 2 H), 4.53 (t, J = 7.5 Hz, 2 H), 5.38 (s, 2 H), 7.18 (d, J = 5.3 Hz, 1 H), 7.27-7.33 (m, 2 H), 7.38-7.39 (m, 1 H), 7.77-7.79 (m, 1 H), 8.34 (d, J = 5.3 Hz, 1 H), 8.74 (s, 1 H);
MS m/e 452 (MH⁺).

20

The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), intranasally, by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

25

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as RSV infection. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

The pharmaceutical composition may be in the form of orally-administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this invention can be administered orally to humans in a dosage range of 0.1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 0.1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 0.1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage

for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the
5 severity of the particular condition, and the host undergoing therapy.

BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial
10 virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at 1.5×10^4 cells/100 μ L/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10% fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 μ L volume in medium
15 containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 μ L at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was
20 aspirated from the cells and 100 μ L/well of acidified isopropanol (per liter: 900 mL isopropanol, 100 mL Triton X100, and 4 mL conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the
25 number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 μ g/mL (corresponding to 10.2 μ M).

30

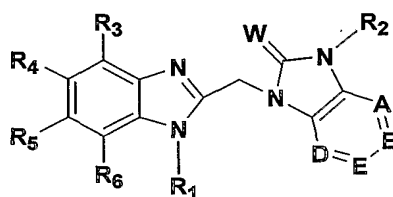
The antiviral activity of compounds, designated as EC₅₀, is presented as a concentration that produces 50% cell protection in the assay. The compounds

disclosed in this application show antiviral activity with EC₅₀s between 50 μ M and 0.001 μ M. Ribavirin has an EC₅₀ of 3 μ M.

CLAIMS

What is claimed is:

- 5 1. A compound having the Formula I, and pharmaceutically acceptable salts thereof,



Formula I

10

wherein:

W is O or S;

- 15 R_1 is $-(CR'R'')_n-X$;

X is H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR''', NR'R'', NR'COR'', NR'CONR''R''', NR'SO₂R'', NR'COOR'', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', PO(OR')₂, aryl, heteroaryl or non-aromatic heterocycle;

20

m is 0-2; n is 2-6;

25

R_2 is

(i) H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl,

$-(CH_2)_t$ C₃₋₇ cycloalkyl, $-(CH_2)_t$ C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is

1-6;

5

(ii) $-(CR'R'')_n-Y$, wherein Y is CN, OR', OCONR'R", NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR''R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂; wherein

10 m is 0-2 and n' is 1-6;

(iii) $-(CR'R'')_n-C_6H_4-Z$, wherein the Z group may be in the ortho, meta or para position relative to the $-(CH_2)_n$ group; Z is CN, OR', OCONR'R", NO₂, NR'R", NCOR', NR'SO₂R", NR'COOR", NR'CONR''R"', COR', CR'''NNR'R", CR'NOR", COOR', CONR'R", SO_mR', SO₂NR'R" or PO(OR')₂;

15

m is 0-2; n" is 0-6; or

(iv) $-(CR'R'')_{n'''}-heteroaryl$, wherein n''' is 0-6;

20

(v) $-(CR'R'')_{n'''}-non-aromatic\ heterocycle$, wherein n''' is 0-6;

R₃, R₄, R₅ and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkyl substituted with one to six of the same or different halogen atoms, OR', CN, COR', COOR', CONR'R", or NO₂;

25

A, B, E, D are each independently C-H, C-Q-, N, or N-O; provided at least one of A, B, E or D is not C-H or C-Q; wherein Q is halogen, C₁₋₃ alkyl or C₁₋₃ alkyl substituted with one to three of the same or different halogen atoms; and

30

R', R'', R''' are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or

different halogen atoms; or R' and R'' taken together form a cyclic alkyl group having 3 to 7 carbon atoms; benzyl, or aryl;

- R''' is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl,
5 NR'R'', CR'NR''R''', aryl, heteroaryl, non-aromatic heterocycle; and

Non-aromatic heterocycle is a 3-7 membered non-aromatic ring containing at least one and up to 4 non-carbon atoms selected from the group consisting of O, S, N, and NR';

10

Aryl is phenyl, naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl;

Heteroaryl is a 4-7 membered aromatic ring which contains one to five heteroatoms independently selected from the group consisting of O, S, N or NR',

- 15 wherein said aromatic ring is optionally fused to group B';

B' is an aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl;

- 20 Aryl, B', said 4-7 membered aromatic ring, and said 3-7 membered non-aromatic ring may each independently contain one to five substituents which are each independently selected from R₇, R₈, R₉, R₁₀ or R₁₁; and

R₇, R₈, R₉, R₁₀ and R₁₁ are each independently

- 25 (i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; and

(ii) halogen, CN, NO₂, OR', NR'R'', COR', COOR', CONR'R'', OCOR', NR'COR'', SO_mR', SO₂NR'R'', PO(OR')₂.

2. The compound of claim 1 wherein heteroaryl is selected from the group
- 5 consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl,
- 10 benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, tetrazole and phenoxazinyl.

- 15 3. A compound of claim 2 wherein:

R₁ is -(CH₂)_n-X;

- X is H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl,
- 20 each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR'', NR'R'', NR'COR'', NR'COOR'', COR', CR''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', aryl or heteroaryl;

- 25 m is 0-2; n is 2-4;

R₂ is

- (i) H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, -(CH₂)_t C₃₋₇ cycloalkyl, -(CH₂)_t C₄₋₇ cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO₂R", SO₂NR'R" or CN; wherein t is 1-6;
- (ii) -(CH₂)_n-Y, wherein Y is CN, OR', COR', COOR', CONR'R", SO_mR', SO₂NR'R", PO(OR')₂ wherein m is 0-2 and n' is 1-6; or
- (iii) -(CH₂)_n"-C₆H₄-Z, wherein the Z group may be in the ortho, meta or para position relative to the -(CH₂)_n" group; Z is CN, OR', COR' or SO_mR'; m is 0-2; n" is 0-3;
- R₃, R₄, R₅, and R₆ are each independently hydrogen, halogen, C₁₋₆ alkyl, optionally substituted with one to six of the same or different halogen atoms; and
- A, B, E, D are each independently C-H or N; provided at least one of A, B, E or D is not C-H.
4. A compound of claim 2 wherein:
- R₃, R₄, R₅ and R₆ are each H;
- A, B and D are each C-H; and
- E is N.
5. A compound of claim 2 wherein:
- R₃, R₄, R₅ and R₆ are each H;
- A, B and E are each C-H; and


D is N.

6. A method for treating mammals infected with RSV, and in need thereof,
which comprises administering to said mammal a therapeutically effective amount
5 of a compound having the Formula I, and pharmaceutically acceptable salts
thereof, as claimed in any one of claims 1-5.
7. A pharmaceutical composition which comprises a therapeutically effective
amount of an anti-RSV compound having Formula I, and pharmaceutically
10 acceptable salts thereof, as claimed in any one of claims 1-5, and a
pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/14775

A. CLASSIFICATION OF SUBJECT MATTER		
IPC(7) : A61K 31/495, 31/50, 31/52, 31/44; A61P 31/12; C07D 471/02, 473/30, 487/02		
US CL : 514/248, 249, 262, 303; 544/236, 265, 276, 350; 546/118		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
U.S. : 514/248, 249, 262, 303; 544/236, 265, 276, 350; 546/118		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CRANK et al., Photochemistry of Heterocycles. III* Photolysis of Various 2-Substituted Benzimidazoles, Australian Journal of Chemistry, 1982, Vol. 35, No. 4, pages 775-784, especially example 5, page 777.	1-7
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search		Date of mailing of the international search report
21 September 2001 (21.09.2001)		25 OCT 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231		Authorized officer
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